

# **Truvada approved as HIV PreP: are South African doctors ready?**

## **Survey measuring willingness to prescribe and attitudes, knowledge, and practises regarding HIV PrEP amongst South African based doctors.**

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I am especially grateful to the doctors who agreed to take the survey and contribute to continuing HIV research, and to God who helps through the good and bad times.

## **DEDICATION**

I dedicate this research report affectionately to the following:

My mother, Mrs Jessica Fleurs who is always there to encourage me and who always urges me to do the best that I can.

My late father, Mr Franklin Fleurs who always supported me and who was always there for me.

## **THESIS ABSTRACT:**

HIV prevention has received renewed attention with the release of results from clinical trials dealing with the efficacy and safety of HIV pre-exposure prophylaxis (PrEP), particularly once daily Truvada, within the last decade.

The results seemed to suggest that PrEP is efficacious with high levels of adherence.

This culminated in the South African Medicines Control Council (MCC) approving use of Truvada as HIV PrEP in December 2015, coupled with the release of SA HIV Clinicians Society guidelines in February 2016.

Several issues were found to be involved in prescribing Truvada as PrEP, including clinical monitoring, adherence counselling, and potential for patient behavioural disinhibition.

The objective of this thesis is to discuss the results of an online survey administered to South African doctors, on their opinions on the use of Truvada as PrEP.

Part A deals with the survey protocol and focuses on (1) ethical issues such as approval by the University of Cape Town Research Ethics Committee, and obtaining consent, (2) method of data collection and (3) procedure of data analysis.

Part B is a literature review expanding on the topics described in the Background section, including extent of problem posed by HIV, failure to develop a viable HIV vaccine, need for HIV PrEP, review of previous research on HIV PrEP, and the need for a study on South African doctors' opinions on PrEP.

Part C is a manuscript that shows the results of the survey, analysis of the data and a discussion on the possible implications.

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## **PART A: PROTOCOL**

### **SYNOPSIS:**

#### **Background and purpose:**

Despite the widespread availability of antiretroviral drugs and extensive research to develop an HIV (human immunodeficiency virus) vaccine, South Africa still has one of the highest HIV rates in the world. Thus, research has continued to find other HIV prevention modalities. These include HIV pre-exposure prophylaxis (PrEP), either taken orally or as a microbicide gel or ring.

Clinical trial data suggests that HIV PrEP is efficacious, but that efficacy depends to a large extent on HIV PrEP client adherence.

The evidence has however been sufficient to justify the approval of Truvada (tenofovir/emtricitabine) as PrEP by the Food and Drug Administration (FDA) on 16 July 2012 in the United States, and more recently by the Medicines Control Council in December 2015 in South Africa (SA). Coupled with this has been the advent of SA HIV Clinicians Society and Centres for Disease Control (CDC) guidelines in 2012 and 2014 respectively.

Implementation of these guidelines however require motivated clinicians who are knowledgeable about the indications for prescribing PrEP, possible side effects, and counselling methods to ensure maximal adherence to the recommended dose of once-daily Truvada..

This preliminary survey thus attempts to monitor whether South African clinicians, are ready to prescribe PrEP to patients.

### **Objectives:**

Main objective is to ascertain how many South African based doctors, are willing to prescribe Truvada as HIV PrEP.

Other objectives are to elucidate knowledge of participating providers about PrEP, barriers and facilitating factors to prescribing PrEP as seen by the participating providers such as concerns about HIV medication resistance, side effects and the belief that prescribing PrEP is the domain of other physicians.

### **Methods:**

#### **Study design:**

The study is a cross-sectional survey that will be administered online.

#### **Selection criteria:**

The population that will be studied are doctors who are members of the South African Medical Association (SAMA).

#### **Recruitment:**

The doctors will be approached via an email sent by SAMA to participate in the proposed online survey. A link to the online survey, will be included in the email.

#### **Consent:**

Consent will be obtained online via a consent form that will be included within the survey.

**Data collection and analysis:**

The online survey was created using the application Survey Monkey. The participants will fill in the survey if they consent, and as each of them submits their responses an online database will be created that will record each response of the participants in a spreadsheet, which can then be exported to Excel.

Exploration of the data will first be performed using means, medians, standard deviations and/or interquartile ranges on single variables that may be predictor variables associated with willingness of the provider to prescribe PrEP.

Logistic regression analysis will then be performed first using univariable analysis and then using multivariable analysis through attempting to build a model using forward selection and selecting predictor variables for inclusion by likelihood ratio testing.

All statistical analyses will be performed using STATA version 12 statistical software, and where applicable graphical representation of data will be performed using Excel 2010.

**Ethical issues:****Potential risks to participants:**

There are no anticipated risks to the participants.

**Protection of confidential information:**

No identifiable information will be entered into the online questionnaire or database at any point.. Access to these will be limited to the investigators, the Faculty of Health sciences Human Research Ethics Committee and other regulatory bodies as applicable.

**Post-trial measures:**

An Ipad can be won by 1 doctor as part of a competition. Also additional literature in the form of a 9 page summary of the current guidelines will be offered to each participant. Each participant will be able to request the information package or to be part of the competition through a separate email sent to the investigators.

## PROBLEM STATEMENT

Human Immunodeficiency Virus (HIV) has remained a significant cause of morbidity and mortality despite decades of research. Research has focussed on treatment and prevention methods such as condom use, and more recently Truvada as HIV pre-exposure prophylaxis.(PrEP).

Use of Truvada as HIV pre-exposure prophylaxis requires motivated clinicians aware of the many associated clinical issues such as monitoring for side effects and counselling to optimize adherence.

The protocol described below thus involves administration of an online survey testing knowledge and opinions of South African doctors on prescription of Truvada as PrEP.

## RESEARCH JUSTIFICATION:

### *Need for HIV pre-exposure prophylaxis*

Despite our modern advances, HIV remains a challenging problem which has eluded all attempts to find a cure or suitable vaccine.

### *Evidence for Truvada as HIV PrEP*

As a result, a number of other approaches, notably use of Truvada as pre-exposure prophylaxis (PrEP) have been attempted to prevent HIV in people at risk.

Recent evidence have suggested that this approach is efficacious. Examples of studies that have demonstrated this include iPrEx study involving 2499 men who have sex with men that showed a reduction in HIV of 44% compared to placebo<sup>1</sup>, the Partners PrEP study involving 4747 heterosexual serodiscordant couples showed a 67% reduction in HIV incidence using oral tenofovir, and a 75% reduction in HIV incidence using oral Truvada, relative to

placebo<sup>2</sup>, The TDF2 study involving 1200 men and women in Botswana taking once-daily oral Truvada showed an efficacy of 62%.<sup>3</sup> and the Bangkok Tenofovir study involving 2413 men and women who injected drugs in Thailand showed a 66% efficacy incidence compared using once-daily oral Truvada as HIV PrEP.<sup>4</sup>

As a result of these and other studies the Medicines Control Council (MCC) in South Africa opted to approve the use of Truvada as PrEP in December 2015.<sup>6</sup> This coincided with the release in February 2016 of the “Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV infection”.<sup>10</sup>

#### *Clinical concerns associated with HIV PrEP*

The guidelines highlight several clinical concerns that clinicians prescribing Truvada as PrEP need to be aware of including monitoring of renal function, bone mineral density, and the importance of monitoring of and ensuring good adherence. Thus motivated and informed clinicians will be crucial to ensuring success of the Truvada PrEP regimen for patients.

#### *Previous research on Truvada as HIV PrEP*

To date, there has not been many studies that assessed knowledge and opinions of doctors on prescribing PrEP, and most have been performed in developed countries notably 2 studies involving a quantitative survey of physicians in Canada<sup>7</sup> and a qualitative survey of American physicians<sup>9</sup>.

The studies mentioned in addition to some others have also added some issues that are pertinent particularly from the point of view of the clinicians that enrolled, in addition to issues mentioned in the South African HIV Clinicians guidelines<sup>10</sup> and CDC guidelines.<sup>5</sup>

These studies show that under 50% of American physicians are willing to prescribe PrEP.<sup>7,8</sup>

The studies, both quantitative and qualitative, also show several perceived barriers to PrEP implementation including logistical concerns associated with monitoring, a feeling that more research still needs to be done to show efficacy, perceived medical risks such as increased HIV resistance if patients become HIV infected, and concerns about patient lack of adherence and possible risk compensation.<sup>7,8,9</sup>

To elucidate further on these concerns and barriers expressed by clinicians in previous surveys, the following factors were noted to reduce potential provider willingness to prescribe PrEP:

- (1) Lack of knowledge of oral PrEP. Surprisingly, 16.5% of providers in a Canadian survey were not familiar with PrEP<sup>7</sup> and 57.5% of healthcare providers in a physician survey conducted in Lima, Peru were aware of PrEP<sup>8</sup>
- (2) Belief that the existing evidence from clinical trials was insufficient to justify widespread prescription<sup>7</sup>
- (3) “Lack of clarity regarding which patient populations were appropriate for PrEP”<sup>7</sup>
- (4) belief by providers that adherence to PrEP would be substantially less in real-world as opposed to clinical trial settings, thus significantly compromising its effectiveness. A concern was also expressed that this would particularly apply to high-risk patients.<sup>9</sup>
- (5) concern about time constraints in busy general practices making adherence and risk reduction counselling suboptimal<sup>9</sup>
- (6) concern about patients not accurately disclosing their sexual behaviour patterns, thus causing providers to potentially miss indications to prescribe PrEP in some cases<sup>9</sup>



- (7) concerns about the high costs of the medication, limiting patients' ability to access Truvada as PrEP <sup>8,9</sup>
- (8) concerns about medication related toxicities, and the belief that patients on PrEP would have a far lower tolerance for these given the fact that they are healthy and HIV negative <sup>9</sup>
- (9) concerns about HIV medication resistance <sup>8,9</sup>
- (10) concerns about patient risk compensation ie engaging in more risky behaviour after starting PrEP <sup>9</sup>
- (11) Inexperience in dealing with the demands created by prescribing PrEP <sup>7</sup>
- (12) the so-called "Purview Paradox" where HIV specialists tended to believe that PrEP should be prescribed by general practitioners as most patients seen by HIV specialists are already HIV positive and do not need PrEP, while in contrast the general practitioners felt that the HIV specialists were more equipped to deal with the monitoring and counselling demands engendered by prescribing PrEP <sup>9</sup>
- (13) Perception by clinicians that potentially eligible clients were not interested in starting PrEP <sup>7,9</sup>

The studies, however, also pointed out several factors that the participating physicians identified would potentially facilitate their willingness to prescribe PrEP.

These factors include:

- (1) belief in the efficacy of PrEP based on previous clinical trial data would create a sense of duty in physicians to prescribe it, despite the problems mentioned above <sup>7,8,9</sup>
- (2) patient motivation, more specifically, patients who were empowered enough to ask physicians about PrEP <sup>9</sup>

- (3) presence of normative guidelines such as those eventually published by the CDC and knowledge that respected peers have already started prescribing PrEP<sup>8,9</sup>

All the research studying physician readiness to prescribe PrEP seems to have been conducted overseas. As South Africa has the highest HIV rate in the world, and PrEP is a powerful tool for prevention of HIV, cooperation of and knowledge of South African doctors or other prescribers is vital to ensure that implementation of existing PrEP guidelines is successful.

There is thus a need for a survey that measures the willingness and attitudes of South African doctors and other types of providers to prescribe PrEP.

This cross-sectional online survey thus attempts to perform a preliminary analysis to ascertain whether South African doctors are willing and ready to prescribe PrEP to their clients.

## OBJECTIVES

1. The primary objective is to establish the willingness of South African based doctors to prescribe HIV PrEP. The method by which this will be done will be described below.
2. Secondary objectives include:
  - To establish whether provider willingness to prescribe PrEP is associated with the proportion of MSM patients in the doctor's practice

- To establish whether provider willingness to prescribe PrEP is associated with the reported percentage of HIV negative patients at high risk of HIV acquisition in the doctor's practice
- To establish whether provider willingness to prescribe PrEP is associated with the doctor's practice serving a high percentage of HIV positive patients
- To establish whether provider willingness to prescribe PrEP is associated with providers self-identifying as HIV experts
- To establish whether being asked about PrEP by one or more patients influences willingness to prescribe PrEP
- To establish whether provider willingness to prescribe PrEP is associated with doctor's opinion on what constitutes an acceptable efficacy
- To assess whether the "purview" paradox, namely that doctors believe prescribing PrEP is the responsibility of other physicians, is present in doctors based in South Africa.

3. Exploratory objectives may include but are not limited to:

- To assess which medium of provider education leads to greater awareness or knowledge of HIV PrEP.
- To assess whether years of experience of a doctor influences willingness to prescribe PrEP.
- To assess whether the sex of a provider influences willingness to prescribe HIV PrEP.
- To assess how many providers agree with the MCC decision to register Truvada as HIV PrEP as well as for HIV treatment.
- To assess whether concerns about the safety of HIV PrEP influences provider willingness to prescribe it.

- To assess whether concerns about the creation of HIV drug resistance on the part of providers will influence willingness to prescribe PrEP.
- To assess whether concerns about patient adherence to Truvada as PrEP will influence doctors' willingness to prescribe PrEP.
- To assess whether other provider demographic factors such as the type of practice influence willingness to prescribe PrEP.
- To assess whether other barriers or facilitating factors identified by providers affect willingness to prescribe PrEP.

## METHODOLOGY

### *Hypotheses*

Hypotheses include:

(1) The primary hypothesis is that at least 40% of South African doctors will be willing to prescribe PrEP. This estimate is based on the results from the previous studies mentioned under "Research Justification" showing willingness to prescribe at over 40% but under 50%.<sup>7,8,9</sup> As South Africa has a much higher HIV prevalence and incidence than the US, it is thus hypothesized that doctors in South Africa will be at least equally willing to prescribe PrEP.

(2) Secondary hypotheses are as follows:

- Doctors who identify themselves as running practices that serve a substantial population of gay, bisexual, and other men who have sex with men as asked in question 17 will be more willing to prescribe PrEP.
- Doctors who serve a high proportion of HIV negative patients at high risk of HIV acquisition will be more willing to prescribe PrEP.

- Doctors who serve a high proportion of HIV positive patients will be more willing to prescribe PrEP.
- Doctors who identify themselves as HIV experts as asked in question 13, will be more likely to prescribe PrEP.
- Doctors who self report at least 1 patient asking them about HIV PrEP as asked in question 22 will be more willing to prescribe PrEP.
- Doctors who believe that at least 60% reduction in HIV incidence constitutes acceptable efficacy, will be less willing to prescribe PrEP.
- It is hypothesized that a “purview paradox” may well be present in the sample of South African doctors, as will be tested by showing that at least 40% of self-identified HIV specialists believe that prescribing PrEP is the responsibility of general practitioners or other specialists, and vice-versa.

Other objectives are exploratory, and thus no formal hypotheses will be stated for them.

### *Study design*

The proposed research study will be a cross-sectional survey, conducted online.

### *Selection of participants*

As this is a preliminary analysis, a sample of doctors based in South Africa will be approached via an online survey. The doctors will be chosen from the South African Medical Association (SAMA) database. South Africa is a very diverse country, with a wide range of people of varying ages, racial groups, occupations and also differing risk of HIV acquisition. For example, there is a relatively high number of vulnerable groups such as men who have sex with men (MSM) and serodiscordant couples.

Thus doctors in South Africa will serve a large number of patients with these characteristics, and will thus be very likely to already be knowledgeable about PrEP and willing to prescribe it due to patient demand.

### *Sampling procedure*

Proportional sampling will be used, by bulk emailing South African doctors who are members of the South African Medical Association, who form a subset of South African doctors who are all required to be registered with the Health Professions Council of South Africa (HPCSA). Each email will contain a message briefly describing the study, and a link to the online survey. A sample copy of the email that will be sent to each doctor is attached as Appendix 1.

From previous studies (Tan and Tang papers) the response rate seems to be about 10%, making an adequate number of completed surveys to analyse and answer the research question.

### *Ethical concerns*

An online consent form will be included after the title page as part of the online survey. The informed consent document is shown in Appendix 2. A block asking whether the study participant agrees to take the survey will need to be ticked before the participant can proceed with the rest of the survey. Failure to tick this box, that is, not giving consent will render the subject unable to continue.

The informed consent document briefly describes the purpose of the study and the rationale for it, namely to assess whether doctors are ready and willing to implement PrEP guidelines and prescribe PrEP now that the MCC has registered use of Truvada as HIV PrEP in South Africa.

The informed consent document also reminds participants of the voluntary nature of the survey. The consent also emphasizes voluntary participation by stating that the survey allows you to not complete the questionnaire without submitting answers at any time before the “done” button is pressed.

Explanation of procedures, that is, instructions to fill in the questionnaire are also included in the informed consent document.

The informed consent document also emphasizes that confidentiality will be maintained at all times. The consent explains that the survey itself does not require the participant to enter any identifying information.

The consent document also goes on to describe that there should be no risk associated with choosing to participate in the study.

The consent form also describes potential benefits of choosing to participate in the survey.

An incentive is provided in the form of being entered into a draw to win an Ipad and/or downloading the new South African guidelines on HIV PrEP<sup>10</sup>. (Appendix 3) In order to receive either of these the participant will be required to send an email to Dr Llewellyn Fleurs stating whether they want to enter the draw for the Ipad or will be able to download literature on HIV PrEP from within the survey, or both. Despite having to send an email to enter the draw for the Ipad, it will not be possible to link the survey responses with any email addresses of the participants.

### *Data collection*

As stated above, an email containing a link to an online survey will be sent to South African doctors who are members of SAMA. The online survey was created by using Survey

Monkey. A copy of the online survey is shown in Appendix 4. A live copy of the survey can also be perused online at <https://www.surveymonkey.com/r/8KW3TNK>

The questionnaire, as per the Tan paper <sup>7</sup>, is divided into 4 domains:

- (a) Demographic and practice based information
- (b) Doctors' knowledge of and experience with HIV PrEP
- (c) Doctor's opinions, beliefs and concerns about PrEP
- (d) Learning needs regarding HIV PrEP identified by the doctors

The questions dealing with the demographics and practice information for each doctor is as below, namely:

Practice location, sex, type of doctor, type of practice, and whether the doctor identifies him/herself as an HIV specialist, the answers of which are recorded as categorical variables. Also, percentage of time spent in clinical activities, years of independent practise, percentage HIV positive patients, percentage high risk HIV negative patients, percentage MSM or intravenous drug users (IDUs).

Questions dealing with doctor's knowledge of HIV PrEP are as follows:

Self-reported knowledge of HIV PrEP (on Likert scale), where the practitioner heard about PrEP, whether the practitioner was questioned by a patient about PrEP, and who asked the doctor about PrEP.

Questions on doctor opinions and beliefs about HIV PrEP are administered as follows:

A question on whether PrEP is dangerous and other statements about PrEP on a Likert scale, what the doctor defines as high risk, whether the doctor agrees with the Medicine Control



Council's (MCC) decision to register Truvada as PrEP, who should pay for it, and who is responsible for prescribing it.

Other questions testing beliefs or opinions include minimum level of efficacy clinicians are willing to accept, how many sexual partners equates to high risk, and how many occasions of unprotected sex the practitioner regards as risky.

Self-identified gaps in knowledge on PrEP is tested for by the following:

A question testing the reaction to statements about PrEP knowledge tested on a Likert scale, media needed to learn more about PrEP, barriers in prescribing PrEP (Likert scale) and support needed to prescribe..

Finally, 2 open-ended questions on what more is needed to implement the new PrEP guidelines, and whether the doctor has any further thoughts to add, are given for possible analysis of further themes that may emerge.

The questionnaire was pilot-tested by individuals working at the Desmond Tutu Vaccine Centre including 3 doctors, our laboratory project manager and data manager for consistency and ease of use.

#### *Data analysis and statistical methods*

Sample size required is as follows:

From the previous studies <sup>7,8</sup> about 50% of doctors +- 10% were willing to prescribe PrEP.

Using the formula  $n = p(1-p) \cdot z^2 / d^2$  where  $p$  is the anticipated population proportion,  $d$  = precision required on either side of the proportion, and  $z$  = the cutoff value of the Normal distribution<sup>11</sup> then the required size to estimate proportion of doctors willing to prescribe PrEP to +-0.1 is 97.

Statistical analyses will be performed as described below:

The outcome variable is what percentage of South African based doctors will be willing to prescribe HIV PrEP to their patients.

Assessing the percentage of doctors willing to prescribe HIV PrEP will be accomplished by tabulating the answers of each doctor to question 31, namely “Knowing what you know now, would you be willing to prescribe PrEP”, and calculating the percentage of doctors willing and unwilling to prescribe PrEP.

Percentages of variables obtained from the question answers, for example, percentage male and female doctors, will be calculated using STATA 12, and the results tabulated.

Box-and-whisker plots will be performed to graphically show any relationship between selected predictor variables, for example, mean minimum acceptable efficacy versus doctor willingness to prescribe PrEP. Significance of any differences in means noted will be tested for using one-way analysis of variance (ANOVA) or unpaired t-tests as appropriate.

Formal hypothesis testing will then be performed using Chi-squared tests and the corresponding odds ratios for the outcome variable and each predictor variable for the following:

- (1) Willingness to prescribe PrEP versus self-identification as an expert in HIV care
- (2) Willingness to prescribe PrEP versus percentage of HIV positive patients in the doctors’ practices. The percentage HIV positive patients will be dichotomized to less than 40% and 40% or above.
- (3) Willingness to prescribe PrEP versus percentage of high risk HIV negative patients in the doctors’ practices. The percentage high risk HIV negative patients will be dichotomized to less than 40% and 40% or above.
- (4) Willingness to prescribe PrEP versus percentage of males who have sex with males (MSM) in the doctors’ practices. The percentage of MSM will be dichotomized to less than 40% and 40% or above.

- (5) Willingness to prescribe PrEP versus being asked by at least one patient about PrEP.
- (6) Willingness to prescribe PrEP versus doctor perception of what constitutes minimum acceptable percentage protection against HIV.
- (7) Willingness to prescribe PrEP versus whether the participating doctors feel that prescribing PrEP is their responsibility or not ( the “purview paradox”<sup>9</sup>).

Where applicable, if any cells in the 2x2 tables have values of 5 or less, Fischer’s exact test will be used instead of the Chi-squared test.

A summary of this hypothesis testing will then be presented.

Graphs plotting answers to Question 44 namely “Please rank the THREE considerations you believe are the MOST IMPORTANT in order from LEAST to MOST important” ie a Likert scale, will be plotted versus willingness to prescribe PrEP.

The data for these graphs will be exported from STATA 12, and Excel 2010 will then be used to further calculate the relevant percentages and plot the resulting graphs.

Logistic regression will then be performed to analyse associations between predictor variables and willingness to prescribe PrEP, and a logistic regression model will then be built using a forward selection strategy. Likelihood ratio tests will be performed and a Chi-squared p-value of 0.05 or less will be used to decide whether variables are included in the model, and p-values of 0.1 used as an exclusion criterion.

The logistic regression model will also be used to derive change in willingness of providers to prescribe PrEP with each 10% increase in reported number of high risk HIV negative patients, each 10% increase in HIV positive patients, each 10% increase in demographic variables such as time spent in clinical work, teaching, public health, and administrative work, each 10 year increase in experience practising independently, and each 10% increase in what constitutes acceptable efficacy for PrEP.

Missing data including respondents not answering the outcome question 31 namely “Knowing what you know about PrEP now, would you prescribe PrEP for a patient at high risk of infection?” will entail an approach using complete case analysis, involving deletion of observations or cases with missing data.

The exception to this will be observations for doctors who stated that they have no previous knowledge of PrEP in response to Question 18: “How would you describe your current knowledge of HIV pre-exposure prophylaxis”, who will be required to skip questions through to Question 30 by the survey. As long as the respondent answered the other questions and the outcome question their observations will not be deleted.

STATA version 12 statistical software will be used for all statistical calculations, and as stated above, Excel 2010 where applicable.

As the emphasis for this dissertation is mainly on quantitative research, the qualitative components of the questionnaire will not be analysed. This, however, may be done at a later stage if analysis of the qualitative component highlights new themes not identified by analysis of the closed questions.

## **PROPOSED BUDGET**

A budget for the proposed study is attached in Appendix 5.

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## **ABBREVIATIONS AND DEFINITIONS**

ANOVA: Analysis of variance

Antiretrovirals: medication normally used to treat HIV, but which can also be used for pre-exposure prophylaxis

CDC: Centres for Disease Control

Efficacy: reduction in HIV percentage resulting from use of PrEP in the exposed group in a clinical trial, compared to those in the trial receiving placebo

HIV: Human Immunodeficiency Virus, the cause of Acquired Immune Deficiency Syndrome

HPCSA Health Professions Council of South Africa

MCC: Medicines Control Council of South Africa

MSM: males who have sex with males

PrEP: pre-exposure prophylaxis, which is the use of medication normally used to treat HIV, but in this case used to prevent HIV and taken before a person is exposed to HIV

PEP: post-exposure prophylaxis, which is use of antiretrovirals for 1 month after an event that potentially exposes a person to HIV

Plasma: part of blood excluding red blood cells



Randomization: random allocation of a study participant to a group

Resistance: non-susceptibility to HIV medications of the HIV virus, in individuals who become HIV positive while on PrEP

SA: South Africa

Seroconversion: person converting from HIV negative to becoming HIV positive

Truvada: combination tablet consisting of the HIV medications tenofovir combined with emtricitabine

US: United States

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### LITERATURE REVIEW

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## OBJECTIVES OF LITERATURE REVIEW:

The objectives of this literature review include:

- (1) Describing the background to the proposed research question, including statistics on the global extent of HIV, and particularly in South Africa.
- (2) Explain the need for approaches to HIV prevention and treatment other than the use of antiretrovirals as treatment, including HIV pre-exposure prophylaxis (PrEP).
- (3) Describe important previous research including clinical trials on the efficacy and safety of PrEP, especially once daily oral Truvada for this indication.
- (4) Explain the rationale behind the Food and Drug Administration (FDA) and Medicines Control Council (MCC) to approve use of once daily oral Truvada as PrEP.
- (5) Detail some of the clinical and logistical issues involved in implementation of Truvada as PrEP.
- (6) Describe previous research on opinions of doctors on prescribing Truvada as PrEP.
- (7) Motivate for a need for a study on provider opinions on PrEP in South Africa.

## SEARCH STRATEGY:

The search strategy employed involved an unsystematic search of Pubmed using the search terms as below:

((HIV vaccine) AND failure) AND (“2” [Date-Publication]:”3000”[Date-Publication]

HIV PrEP and knowledge; (HIV PrEP) AND acceptability; ((HIV PrEP) AND adherence) AND efficacy; South African women AND HIV PrEP; (Questionnaires) AND HIV PrEP; ((gaps) AND research) AND HIV PrEP

Provider knowledge about HIV PrEP; physicians attitudes about HIV PrEP; provider practices about HIV PrEP; doctor practices about HIV PrEP; survey HIV PrEP; FDA approval Truvada PrEP; cost-effectiveness of PrEP; adolescents AND PrEP; RV144.

A search on Google was also performed for “HIV in South Africa” and “population in provinces in South Africa”.

## LITERATURE SUMMARY:

### Background: need for HIV PrEP

#### *Relevant HIV statistics*

To start off with, HIV is still an important problem that needs intervention in today's modern world. To illustrate this point, the following statistics on HIV are given in the references discussed below.

Globally, WHO estimates that 34.3 million adults were living with HIV in 2014, of which 17.4 million were women.. Furthermore, 1.8 million adults were newly infected, and 1 million adults died in 2014. <sup>1</sup>

Stats SA estimates that over 458933 deaths occurred in South Africa in 2013 and that 51.2% of these deaths are found in the 15 to 59 year age groups. The article also shows that HIV gave rise to 17338 deaths (3.4%) in 2011 and this increased to 23201 deaths (5.1%) in 2013. <sup>2</sup>

Prevalence rates of HIV in South Africa in 2012 vary by province as follows in descending order:

Kwazulu Natal with 16.9%, Mpumalanga with 14.1%; Free State with 14%; North West Province with 13.3%; Gauteng with 12.4%; Eastern Cape with 11.6%; Limpopo Province with 9.2%; Northern Cape with 7.4% and Western Cape with 5%.

South African women are also affected disproportionately by HIV with the prevalence in this group aged 15 to 49 being 18.99% while those for adults at same age range is 16.59%. Adolescents also contribute significantly to the HIV burden with a prevalence of 5.59%.<sup>3</sup>

#### *Limited success of antiretrovirals*

“Physicians now have approximately 30 antiretroviral products” which coupled with diagnostic modalities like PCR have decreased the prevalence and incidence of HIV/AIDS.

To illustrate this decrease, the following statistics are pertinent:

HIV/AIDS was the leading cause of death in the 25 to 44 year age group in 1995 in the US, resulting in 32000 deaths or 20% of all deaths in this age group. By 2005, this had decreased to 6000 deaths or 5% of all deaths in this age group. Also, HIV positive patients live up to 14 years longer as a result of widespread antiretrovirals.

“Access to antiretroviral agents also leads to improvements in outcomes for HIV-1/AIDS patients in resource-poor countries.”<sup>4</sup>

Despite these successes several challenges still remain.

- (1) Increased mortality despite HAART can still occur in people with common comorbid conditions. For example, a study, found that 15 out of 102 participants with concomitant TB died (15%), while 41 out of 1413 patients with no concomitant disease died (3%).
- (2) Pre- and post-integration latency.

“As a rule, viral rebound follows discontinuation of therapy, and on that account, therapy must be undertaken for a lifetime.”<sup>4</sup>

- (3) HIV is now considered a chronic disease. HAART with extended survival can result in long-term sequelae, which need to be managed. “In this context, ..... which can in turn increase the risk for developing heart disease and type 2 diabetes”. <sup>4</sup>
- (4) Treatment of paediatric HIV patients remains problematic. <sup>4</sup>
- (5) Despite our successes, the WHO statistics mentioned above are sobering. <sup>1</sup>

#### *Failure to develop an HIV vaccine*

Allied to HIV still significantly contributing to global mortality despite wider use of antiretrovirals, is the failure to develop an effective candidate vaccine, despite decades of research.

Only the RV144 clinical trial testing “canarypox recombinant vector vaccine ALVAC-HIV (vCP1521) and recombinant gp120 AIDSVAX B/E administered in a prime-boost HIV vaccine regimen showed a reduction of HIV incidence of 31% in the vaccine compared to the placebo group in 2009,<sup>5</sup> and only recently did a candidate subtype C gp140 vaccine primed by SAAVI DNA-C2 and boosted by MVA-C HIV vaccine show CD4 and CD8 T-cell responses of “74% and 32% of the participants, respectively in April 2016..”<sup>6</sup>

#### *Challenges involved in development of an HIV vaccine*

There are several challenges involved in the development of an HIV vaccine. These include:

- (1) the “exact immune correlates of natural HIV protection are poorly defined
- (2) extensive genetic diversity of HIV subtypes (3) need for HIV vaccines for Africa to be capable of inducing specific CD4 T-cell responses that enhance both CD8 T-cell and humoral antibody responses, (4) need for HIV vaccines to induce a good mucosal T and B-cell response<sup>7</sup>

All the above, underscores the fact that investigating other HIV prevention methods other than vaccines is still of paramount importance, including HIV PrEP.

#### *Efficacy of HIV PrEP: successes*

Several studies using either Tenofovir or Truvada as HIV PrEP, either taken orally or used as a microbicide gel have been conducted. The most noteworthy are detailed below:

The CAPRISA004 study was conducted in May 2007 to March 2010 in Kwazulu-Natal, South Africa. Enrolled women were randomized to 2 arms: tenofovir gel or placebo gel. Results showed that use of a peri-coital microbicide gel in 889 South African women produced a “reduction of HIV incidence of 54% in high gel adherers, and 38% and 28% in intermediate and low gel adherers”.<sup>8</sup>

The multinational iPrEx study involved 2499 men who have sex with men, conducted from July 2007 through December 2009, who were assigned randomly to receive either Truvada or placebo. Out of 100 seroconverters, 36 became infected in the Truvada group, and 64 became infected in the placebo group, giving an efficacy of 44%.<sup>9</sup>

The Partners PrEP study conducted from July 2008 through November 2010 in Kenya and Uganda involved 4747 heterosexual serodiscordant couples. The HIV negative participants were randomized to receive once-daily tenofovir, Truvada or placebo. There was a 67% reduction in HIV incidence using oral tenofovir, and a 75% reduction in HIV incidence using oral Truvada, relative to placebo.<sup>10</sup>

The CDC 4940 (TDF2) study involving 1200 men and women in Botswana taking once-daily oral Truvada showed an efficacy (reduction in HIV incidence compared to placebo) of 62%.<sup>11</sup>

The Bangkok Tenofovir study involving 2413 men and women who injected drugs in Thailand showed a 66% efficacy ( reduction in HIV incidence compared to placebo) using once-daily oral Truvada as HIV PrEP. <sup>12</sup>

#### *Efficacy of HIV PrEP: failures*

In contrast, however, some studies testing use of tenofovir or Truvada as HIV PrEP showed no efficacy.

An example of these are the FEM-PrEP study involving 1950 women from Africa, Kenya, and Tanzania conducted in June 2009 through April 2011, who were randomized to receive either Truvada or placebo. The study showed a 6% efficacy ( 33 HIV infections in the Truvada group and 35 in the placebo group).<sup>13</sup>

Another example is the VOICE study involving 5029 women from South Africa, Uganda, and Tanzania conducted from September 2009 through June 2011. The participants were randomized in a 1:1:1:1:1 ratio into 5 groups: oral tenofovir with Truvada placebo, oral Truvada and tenofovir placebo, oral tenofovir placebo with Truvada placebo, vaginal 1% tenofovir gel and vaginal placebo gel. 312 seroconversions occurred in the study and were included in the primary analysis, yielding 52 in the tenofovir group, 61 in the Truvada group, 61 in the tenofovir gel group, 60 in the oral placebo group, and 70 in the placebo group. The efficacy was thus -4.4% for once-daily oral Truvada, -49% for once-daily oral tenofovir, and 15% efficacy for daily vaginal tenofovir gel use. <sup>14</sup>

#### *Adherence as explanation for discrepancies in efficacy*

One of the most plausible explanations for the discrepant results noted in these trials is substantial differences in adherence to the study regimens.

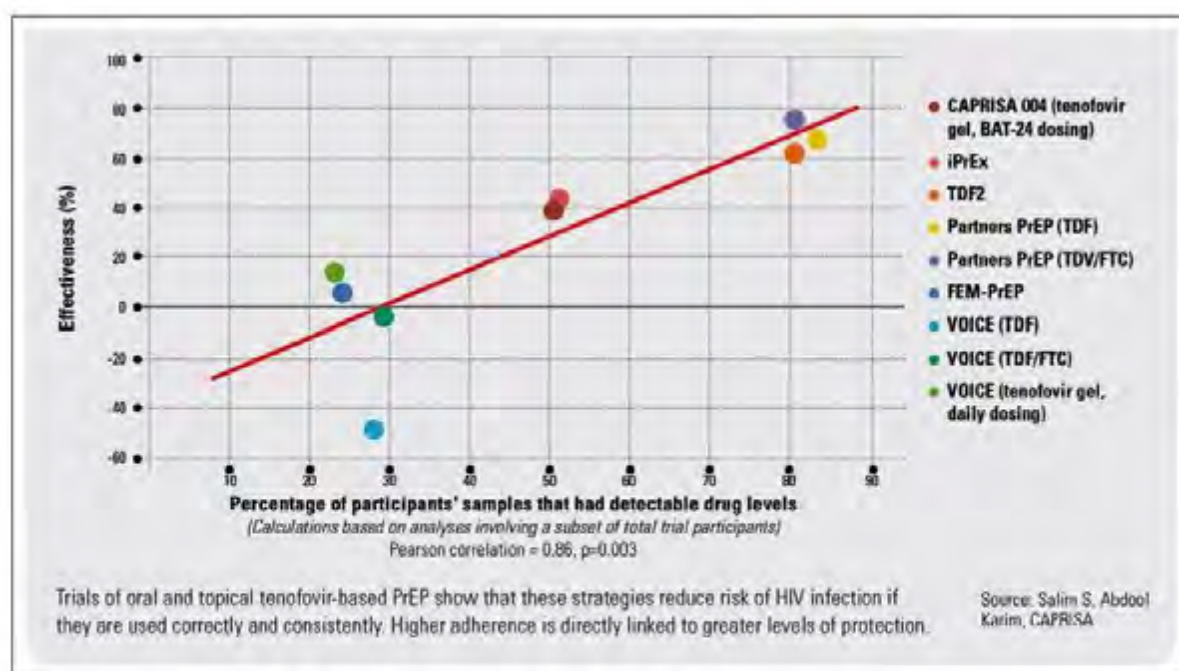


To show evidence for this statement, the adherence statistics in each of the trials mentioned above is illustrated below:

For the studies which demonstrated efficacy, the CAPRISA004 study recorded 72.% of sex acts covered by use of tenofovir gel before and after coitus and was similar in either gel or placebo group; <sup>8</sup> the iPrEx study recorded self-reported pill use and stable use of drug from 8 weeks post-enrollment measured by pill count of at least 89% in each group; <sup>9</sup> the Partners PrEP study indicated by pill count that at least 97% of tablets in either group were taken , <sup>10</sup> TDF2 study showed adherence rates of 81%, <sup>11</sup> and the Bangkok Tenofovir Study showed adherence rates of 66%.<sup>12</sup>

In contrast, for the studies which demonstrated no efficacy, adherence rates for the FEM-PrEP study was 7 out of 27 ie 26% for women who seroconverted as measured by plasma tenofovir level, <sup>13</sup> and for the VOICE study mean plasma tenofovir was 29% for Truvada use, 30% for tenofovir use and 25% for vaginal tenofovir gel use. <sup>14</sup>

A graphical representation showing the linear relationship between the degree of adherence versus the efficacy is shown below: (ref 20)



Source: AVAC Report 2013: Research & Reality [http://www.avac.org/sites/default/files/infographics/PrEP\\_by\\_Numbers\\_jan2016.jpg](http://www.avac.org/sites/default/files/infographics/PrEP_by_Numbers_jan2016.jpg)  
FIGURE 1: Effectiveness and adherence in trials of oral and topical tenofovir-based prevention.

<http://www.sajhivmed.org.za> Open Access

The correct conclusion thus seems to be that HIV PrEP is efficacious, but that the efficacy depends on adherence of patients or participants.

### *Safety data on HIV PrEP*

The studies also showed that use of Truvada or tenofovir as HIV PrEP was reasonably safe.

The safety data is as follows:

CAPRISA004 showed “Coitally-related tenofovir gel use was safe. There were no increases in renal, hepatic, pregnancy-related or genital adverse events” with only increased diarrhoea noted as an adverse event possibly related to the gel.<sup>8</sup> iPREx showed “In testing for elevations in serum creatinine levels, there were 41 instances of elevations that were at least 1.1 times the upper limit of the normal range or more than 1.5 times the baseline level”<sup>9</sup> resulting in 10 permanent discontinuations of study drug. All these creatinine elevations were however reversible, with study drugs being restarted in 9 subjects.

Nausea also occurred more in the exposed as opposed to the placebo group.<sup>9</sup> Other adverse events noted in these trials were:

- Statistically significant declines in bone mineral density in the TDF2 study
- “Pre-existing HIV infection” documented in every study PrEP study
- Development of “treatment related resistance” in “a small amount of HIV seroconverters”, mainly resistance mutations implicated in emtricitabine resistance<sup>15</sup>

Additional data shows that HIV PrEP including other PrEP modalities may be efficacious and safe:

- (1) HPTN067 randomized 179 Cape Town based women to use of TDF/FTC daily, twice weekly with post-sex cover, and before and after sex. Results showed only 1/60 participants; and 2/60 and 2/60 participants respectively in each group seroconverted. Adherence was lower however in the time-driven and event-driven groups (76%, 65% and 53% respectively).<sup>29</sup>
- (2) The PROUD and IPERGAY studies enrolled men who have condomless anal sex in trials in the United Kingdom and France respectively, and randomized them to once daily TDF/FTC or placebo. Results indicated a relative risk reduction of TDF/FTC versus placebo of 86%.<sup>30,31</sup>
- (3) MTN020 and IPM027 tested the efficacy and safety of a monthly Dapivirine ring versus placebo, and showed a relative risk reduction of HIV-1 of Dapivirine versus placebo of 27% (95% CI 1 to 46 p=0.046) and 30.7% (95% CI 0.90 to 51.5 p=0.0401)<sup>31</sup>
- (4) The Partners Demonstration Project involving administering antiretrovirals to the HIV positive partners in serodiscordant couples, and PrEP to the HIV negative partners showed only 5 incident infections out of 1013 participants, far below the projected 63 infections.<sup>30</sup>

- (5) Long-acting injectable PrEP regimens involving rilpivirine, maraviroc and cabotegravir have to date also been safe and well tolerated.<sup>31</sup>
- (6) Caution, however, needs to be exercised in certain situations regarding PrEP use as has been demonstrated in some clinical trials. The IPrEx open-label extension suggested that long-term exposure to TDF/FTC as PrEP may be associated with declining renal function over time<sup>30</sup>, the US Demo Project showed that more careful monitoring of younger PrEP users and those with diabetes and hypertension may be warranted<sup>31</sup>.

#### *Regulatory body approvals for Truvada as HIV PrEP*

Given the public health importance of finding HIV prevention or treatment modalities to supplement the existing HAART regimens, the lack of success in developing an HIV vaccine, and the available evidence, the FDA approved use of oral daily Truvada as HIV PrEP on 16 July 2012.<sup>16</sup>

#### *Release of guidelines on use of HIV PrEP*

FDA registration of PrEP was further backed up in the United States by the release of guidelines developed by the Centres of Disease Control (CDC), detailing the indications for prescribing PrEP, allied monitoring and counselling, and special considerations (for example, interactions with other medications) in 2014.<sup>17</sup>

Guidelines for use in males who have sex with males (MSM) were released in South Africa prior to the CDC guidelines.<sup>18</sup>

The World Health Organization (WHO) conducted a review of 12 randomized controlled trials on the effectiveness of oral PrEP, agreed that level of protection offered by PrEP is strongly correlated to adherence, and that “use of daily oral pre-exposure prophylaxis (PrEP) is recommended as a prevention choice for people at substantial risk of HIV infection.”

Substantial risk was defined as risk leading to an incidence of HIV infection in the absence of PrEP that is sufficiently high (>3% incidence) to make offering PrEP potentially cost-effective. These risk groups included MSM, transgender women and uninfected partners in serodiscordant couples.<sup>28</sup>

Review of all these guidelines has now culminated in the Medicines Control Council in South Africa approving HIV PrEP as a registered medicine in South Africa.<sup>19</sup> Previously PrEP was only prescribed off label in South Africa. More recently in February 2016, the updated “Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV infection” were released, which now covers both MSM and other people at risk of HIV.<sup>20</sup>

Despite the evidence for the efficacy of PrEP, there are several issues that clinicians need to be aware of when trying to implement these new PrEP guidelines.

### *Issues associated with prescribing PrEP*

One of the first issues is awareness of the appropriate indications for prescribing PrEP.

In this regard, the CDC and updated South African guidelines are very detailed, and each have a list of indications for prescribing PrEP for MSM, intravenous drug users, and heterosexuals.<sup>17,20</sup>

Some of the clinical issues identified by both guidelines include:

- (1) Mandatory baseline investigations including renal function tests, hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb) and a sexually transmitted infections (STI) screen<sup>17,18,20</sup>
- (2) Recommended medications for HIV PrEP only include tenofovir and Truvada<sup>17</sup>
- (3) Regular monitoring needed. Similar clinical monitoring schedules are mentioned in all guidelines, requiring monitoring of clients at screening, initiation of HIV PrEP, 1 month, 4 months post-initiation and 6-monthly STI screen and annual renal function screening.<sup>17,18,20</sup>
- (4) Only clients with a creatinine clearance of 60ml/min or more should be started on PrEP<sup>17,18,20</sup>
- (5) Need to treat gastrointestinal symptoms and other minor side effects symptomatically<sup>18,20</sup>
- (6) Close monitoring for major side effects, for example, renal failure hinted at above or bone mineral density decrease, especially in persons with a family history of osteoporosis or pathological fractures<sup>17,18,20</sup>
- (7) Need to monitor for acute flare-ups of hepatic dysfunction when tenofovir or Truvada is withdrawn in patients with chronic active hepatitis, for example, due to poor patient adherence.<sup>17,18,20</sup>
- (8) Need to attempt to prevent HIV medication resistance as much as possible by withdrawing HIV PrEP if symptoms and signs consistent with acute HIV seroconversion syndrome is noted in a patient.<sup>18,20</sup>

Thus counselling to ensure that the patient remains motivated and adherent is of paramount importance. Strategies to achieve high adherence levels and prevention of increasing risky behaviour (risk compensation) while on PrEP is thus mentioned in all guidelines.

These strategies include:

- (1) Need for an individualised risk benefit assessment to assess participant eligibility for PrEP<sup>17,18,20</sup>
- (2) Need for implementation of risk reduction counselling together with adherence counselling at all follow-up visits.<sup>18,20</sup> To this effect, the guidelines have also given an series of strategies toward improving medication adherence.<sup>17,20</sup>
- (3) It is to be noted that the new South African guidelines talk about “effective use” and not adherence, as these guidelines do not envisage that people will use HIV PrEP lifelong as with antiretrovirals used therapeutically, but only during periods in their lives where their risk of HIV acquisition is high.<sup>20</sup>

#### *Previous research on provider opinions regarding PrEP*

Due to the fact that PrEP is highly dependant on good adherence for efficacy, as shown by the clinical trials described above, and that the successful implementation of PrEP requires knowledge of PrEP and attendant medical and other issues and commitment by physicians several studies were done to assess physician readiness to prescribe PrEP mainly in the United States. These studies were conducted prior to the FDA decision to approve Truvada as PrEP and the later release of the CDC guidelines.

These studies show that under 50% of American physicians are willing to prescribe PrEP.

<sup>21,22</sup> The studies, both quantitative and qualitative, also show several perceived barriers to PrEP implementation including logistical concerns associated with monitoring, a feeling that

more research still needs to be done to show efficacy, perceived medical risks such as increased HIV resistance if patients become HIV infected, and concerns about patient lack of adherence and possible risk compensation.<sup>21,22,23</sup>

To elucidate further on these concerns and barriers expressed by clinicians in previous surveys, the following factors were noted to reduce potential provider willingness to prescribe PrEP:

- (14) Lack of knowledge of oral PrEP. Surprisingly, 16.5% of providers in a Canadian survey were not familiar with PrEP<sup>21</sup> and 57.5% of healthcare providers in a physician survey conducted in Lima, Peru were aware of PrEP<sup>22</sup>
- (15) Belief that the existing evidence from clinical trials was insufficient to justify widespread prescription<sup>21</sup>
- (16) “Lack of clarity regarding which patient populations were appropriate for PrEP”<sup>21</sup>
- (17) belief by providers that adherence to PrEP would be substantially less in real-world as opposed to clinical trial settings, thus significantly compromising its effectiveness. A concern was also expressed that this would particularly apply to high-risk patients.<sup>23</sup>
- (18) concern about time constraints in busy general practices making adherence and risk reduction counselling suboptimal<sup>23</sup>
- (19) concern about patients not accurately disclosing their sexual behaviour patterns, thus causing providers to potentially miss indications to prescribe PrEP in some cases<sup>23</sup>



- (20) concerns about the high costs of the medication, limiting patients' ability to access Truvada as PrEP <sup>22,23</sup>
- (21) concerns about medication related toxicities, and the belief that patients on PrEP would have a far lower tolerance for these given the fact that they are healthy and HIV negative <sup>23</sup>
- (22) concerns about HIV medication resistance <sup>22,23</sup>
- (23) concerns about patient risk compensation ie engaging in more risky behaviour after starting PrEP <sup>23</sup>
- (24) Inexperience in dealing with the demands created by prescribing PrEP <sup>21</sup>
- (25) the so-called "Purview Paradox" where HIV specialists tended to believe that PrEP should be prescribed by general practitioners as most patients seen by HIV specialists are already HIV positive and do not need PrEP, while in contrast the general practitioners felt that the HIV specialists were more equipped to deal with the monitoring and counselling demands engendered by prescribing PrEP <sup>23</sup>
- (26) Perception by clinicians that potentially eligible clients were not interested in starting PrEP <sup>21,23</sup>

The studies, however, also pointed out several factors that the participating physicians identified would potentially facilitate their willingness to prescribe PrEP.

These factors include:

- (4) belief in the efficacy of PrEP based on previous clinical trial data would create a sense of duty in physicians to prescribe it, despite the problems mentioned above <sup>21,22,23</sup>
- (5) patient motivation, more specifically, patients who were empowered enough to ask physicians about PrEP <sup>23</sup>

(6) presence of normative guidelines such as those eventually published by the CDC and knowledge that respected peers have already started prescribing PrEP<sup>22,23</sup>

All the research studying physician readiness to prescribe PrEP seems to have been conducted in the US. As South Africa has the highest HIV rate in the world, and PrEP is a powerful tool for prevention of HIV, cooperation of and knowledge of South African doctors or other prescribers is vital to ensure that implementation of existing PrEP guidelines is successful.

#### *Controversies surrounding HIV PrEP*

Since the approval of Truvada as PrEP and the attendant guidelines, several non-clinical issues have been raised related to implementation. Some of these issues include cost-effectiveness of scaling up Truvada as PrEP, and the case for investment required for implementation, particularly in South Africa.

In the South African TB and HIV Investment Case Report<sup>24</sup> PrEP for sex workers, discordant couples, adolescents and microbicides was discussed. The report identified unit costs and so-called “Technical Efficiency” factors for these and other interventions. The available evidence suggests that “once daily Truvada is needed to offer protection from HIV.”<sup>24</sup> Ensuring adherence was identified as a key Technical Efficiency factor, and the importance of effective adherence counselling was highlighted.

The existing and future health budgets will have to cover the costs of scaling up interventions such as PrEP, and cost-effectiveness of PrEP programs has thus become a major point of discussion.

Pretorius et al.<sup>25</sup> highlight that even assuming that PrEP will cost \$150 per year per person, as compared to antiretrovirals costing \$600 per year per person, “expanding ART would still prove more effective in terms of cost per infection averted”, and that the cost would be \$12500 to \$20000 per infection averted from 2014 to 2025. The cost-effectiveness would be adversely affected if antiretroviral coverage and behavioural disinhibition increases during scale up of PrEP.<sup>25</sup>

To counter this cautious viewpoint, targeting high risk groups was however identified as enhancing the effectiveness of any PrEP program, and being more cost-effective.<sup>24</sup> Thus allied to the MCC decision on PrEP, the South African Minister of Health in his budget speech on 10 May 2016, approved administering oral Truvada as PrEP in selected countrywide sex worker programmes along with universal access to testing and treatment.<sup>26</sup>

Other observers, notably Professor Bekker et.al<sup>27</sup> have noted that adolescents constitute another vulnerable group, as seen by the HIV prevalence of 5.59% noted previously.<sup>3</sup> A number of reasons such as power inequality particularly with intergenerational sex, and intimate partner violence have been given for this vulnerability. However, studies such as the ADAPT study involving regimens comprising self-administered daily, event-driven and intermittent Truvada as PrEP showed similar adherence between younger and older participants. This group therefore advocates more research and availability of PrEP for this vulnerable group.<sup>27</sup>

### **Motivation for proposed study**

There is thus a need for a survey that measures the willingness and attitudes of South African doctors and other types of providers to prescribe PrEP.

The survey thus tests opinions of South African doctors on Truvada as PrEP, and tries to ascertain whether clinical and/or non-clinical issues that could relate to the technical efficiency factors noted above affect willingness to prescribe PrEP on the part of South African doctors. Results and the associated discussion are detailed in the Manuscript section below.

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## **PART C: MANUSCRIPT**

### **Abstract:**

#### *Introduction*

Recent clinical trials has demonstrated the efficacy of use of Truvada as pre-exposure prophylaxis (PrEP) in preventing HIV infection. The Medicines Control Council accordingly approved use of once daily Truvada as PrEP in December 2015. To date no African studies have been done measuring knowledge and attitudes of clinicians on this topic.

#### *Methods*

Thus, an online survey was administered from 21 June till 14 July 2016, inviting doctors on the South African Medical Association database, a subset of all South African doctors who are all required to be registered with the Health Professions Council of South Africa (HPCSA) to participate.

#### *Results*

289 out of 14325 doctors (2%) responded to the survey. Results show that approximately 74% of respondents were willing to prescribe Truvada as PrEP. Hypothesis testing showed that provider willingness to prescribe PrEP was associated with serving a relatively high proportion of MSM patients, self-identification as an expert in HIV care and being questioned about PrEP by at least one patient. All respondents rated efficacy, development of HIV resistance, compliance of patients, and logistics of monitoring for clinical complications as major concerns in deciding to prescribe PrEP to patients. Other concerns noted included possible sexual disinhibition of patients, access to PrEP for patients and cost-effectiveness, particularly in those doctors who were ambivalent about prescribing Truvada as PrEP. Certain facilitating factors were also noted by the respondents as potentially having the effect of increasing their willingness to provide Truvada as PrEP, namely availability of qualified counsellors for adherence counselling, availability of nurses to assist with clinical monitoring of patients, and more continuing medical education on PrEP.

#### *Conclusions*

South African doctors are willing to face the challenge embodied in implementation of prescribing Truvada as PrEP.

## Introduction

Despite our modern advances, HIV remains a challenging problem which has eluded all attempts to find a cure or suitable vaccine.

Thus, a number of other approaches, notably use of Truvada as pre-exposure prophylaxis (PrEP) have been attempted to prevent HIV in people at risk.

Recent evidence have suggested that this approach is efficacious. Examples of studies that have demonstrated this include the iPrEx study that showed a reduction in HIV of 44% compared to placebo[1], the Partners PrEP study that showed a 67% reduction in HIV incidence using oral tenofovir, and a 75% reduction in HIV incidence using oral Truvada, relative to placebo[2], the TDF2 study that showed an efficacy of 62%,[3] and the Bangkok Tenofovir study that showed a 66% efficacy incidence compared using once-daily oral Truvada as HIV PrEP. [4]

As a result of these and other studies the Medicines Control Council (MCC) in South Africa opted to approve the use of Truvada as PrEP in December 2015.[5] This coincided with the release in February 2016 of the “Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV infection”.[8]

The guidelines highlight several clinical concerns that clinicians prescribing Truvada as PrEP need to be aware of including monitoring of renal function, bone mineral density, and the importance of monitoring of and ensuring good adherence. Thus motivated and informed clinicians will be crucial to ensuring success of the Truvada PrEP regimen for patients.

To date, there has not been many studies that assessed knowledge and opinions of doctors on prescribing PrEP, and most have been performed in developed countries notably 2 studies involving a quantitative survey of physicians in Canada[6] and a qualitative survey of American physicians[7]. No African equivalent to these studies has to date been done. This study, which is a quantitative survey of South African doctors, was thus designed to attempt to address this research gap.

**Methods:**

The primary objective is to establish the willingness of South African based doctors to prescribe HIV PrEP, with subsequent analyses performed to ascertain the association of putative predictor variables such as doctors serving a high proportion of high risk HIV negative patients with willingness to prescribe PrEP. The method by which this will be done will be described below.

Doctors who were members of the South African Medical Association (SAMA) were invited to take an online survey, and responses collected from 21 June 2016 till 14 July 2016, using a sampling frame of doctors belonging to the South African Medical Association (SAMA), ie a proportion of total South African doctors registered with the Human Professions Council of South Africa (HPCSA)..

Ethical approval for the study was obtained from the University of Cape Town Human Research Ethics Committee (Appendix 6). The presentation of the research was optimized according to Journal of the International AIDS Society guidelines (Appendix 7).

Sample size required was calculated at 97, using the following formula:

$n = p(1-p) \cdot z^2 / d^2$  where  $p$  is the anticipated population proportion,  $d$  = precision required on either side of the proportion, and  $z$  = the cutoff value of the Normal distribution.[9]

As per the Tan paper [6] the online questionnaire was divided into domains eliciting the willingness to prescribe Truvada as PrEP, demographic details of the doctors; their knowledge on PrEP; their perception of barriers, concerns and facilitating factors associated with their willingness to prescribe Truvada as PrEP as rated using Likert scales; and their perceived learning needs.

These responses were then analysed using STATA12, and graphical representation of the analyses of opinions expressed on provision of PrEP and perceived barriers to prescribing PrEP were plotted using Excel 2010.



Testing of main hypotheses was also performed using chi-squared tests to test association of provider willingness to prescribe PrEP against proportion of patients who are males who have sex with males (MSM), and high risk HIV negative patients. The association between willingness to prescribe PrEP was also tested against being asked about PrEP by a patient, self-identification as an HIV expert, amount of reduction in HIV incidence using PrEP that is the minimum acceptable, and the so-called “purview paradox”<sup>7</sup> where doctors feel that it is not their responsibility to provide PrEP.

Predictor variables where applicable, were dichotomized as follows for the hypothesis testing:

Less than 40% and at least 40% HIV positive patients served, the same categories for proportion of HIV negative patients served, and less than 60% and at least 60% for minimum acceptable efficacy.

A similar method was used to conduct exploratory hypothesis testing in order to accomplish the secondary objectives outlined above. Similarly, predictor variables were dichotomized where applicable, namely less than 3 years or at least 3 years independent practice.

A logistic regression using a forward selection procedure was performed on the observations generated by the survey respondents, and observations with missing data excluded using a complete case analysis approach.

Both the hypothesis testing and logistic regression were performed using STATA12.

## **Results:**

### *Amount of respondents*

289 out of 14325 doctors who were SAMA members responded ie a 2% response.

### *Demographics*

The following demographic characteristics were noted, as detailed in Table 1:

Most doctors were from provinces with a high degree of urbanization, for example, Western Cape, Gauteng and Kwazulu Natal.

Sex of the respondents were relatively evenly distributed with 55.06% being female, and 44.94% being male.

Most of the doctors were also general practitioners, and about 69% work in the public sector, with approximately 60% being independent practitioners for more than 5 years.

The mean proportion of HIV positive patients served by the responding doctors was 37.70%, while the mean proportion of high risk HIV negative doctors served was 32.28%.

#### *Willingness to prescribe*

Of the responding doctors, approximately 74% expressed a willingness to prescribe Truvada as PrEP, with approximately 26% being undecided or unwilling to prescribe Truvada as HIV PrEP.

Gratifyingly, although 26 doctors (9%) did not know about Truvada being approved as PrEP, only 3 did not answer the outcome question, with 13 (50%) saying “Yes” and 10 (38%) answering “Maybe”.

**Table 1: Univariable analysis for South African doctor survey on HIV PrEP**

Question	Description	Number	Total	%
<b>Demographics</b>				
Location of practice	Western Cape	49	245	20.00
	Gauteng	75	245	30.61
	Eastern Cape	27	245	11.02
	Kwazulu Natal	46	245	18.78
	North West Province	12	245	4.90
	Mpumalanga	12	245	4.90
	Free State	10	245	4.08
	Limpopo	8	245	3.27
	Northern Cape	6	245	2.45
Sex	Male	111	247	44.94
	Female	136	247	55.06
Type of physician	Infectious disease specialist	2	246	0.81
	Non-specialist in infectious diseases	243	246	99.19
	Specialist in HIV care	55	246	22.36
	Non-specialist in HIV care	191	246	77.64
Type of practice	Private sector	77	246	31.30
	Public sector	169	246	68.70
% time spent on activities	Mean time spent on clinical activities (%)	N/A	242	73.71
	Mean time spent on research activities (%)	N/A	238	4.65
Experience	Independent practise for $\geq 5$ years	146	242	60.34
	Independent practise for $< 5$ years	61	242	25.20
	Intern/ community service	35	242	14.46
Distribution of patients	Mean proportion HIV positive (%)	N/A	243	37.70
	Proportion high risk HIV negative (%)	N/A	236	32.28
<b>Opinions about HIV PrEP</b>				
Willingness to prescribe PrEP	Yes	157	213	73.71

	Maybe	51	213	23.94
	No	5	213	2.35
<b>Familiarity with PrEP</b>				
Current knowledge	Very familiar	39	246	15.85
	Limited familiarity	181	246	73.58
	No familiarity	26	246	10.57

### *Familiarity with PrEP*

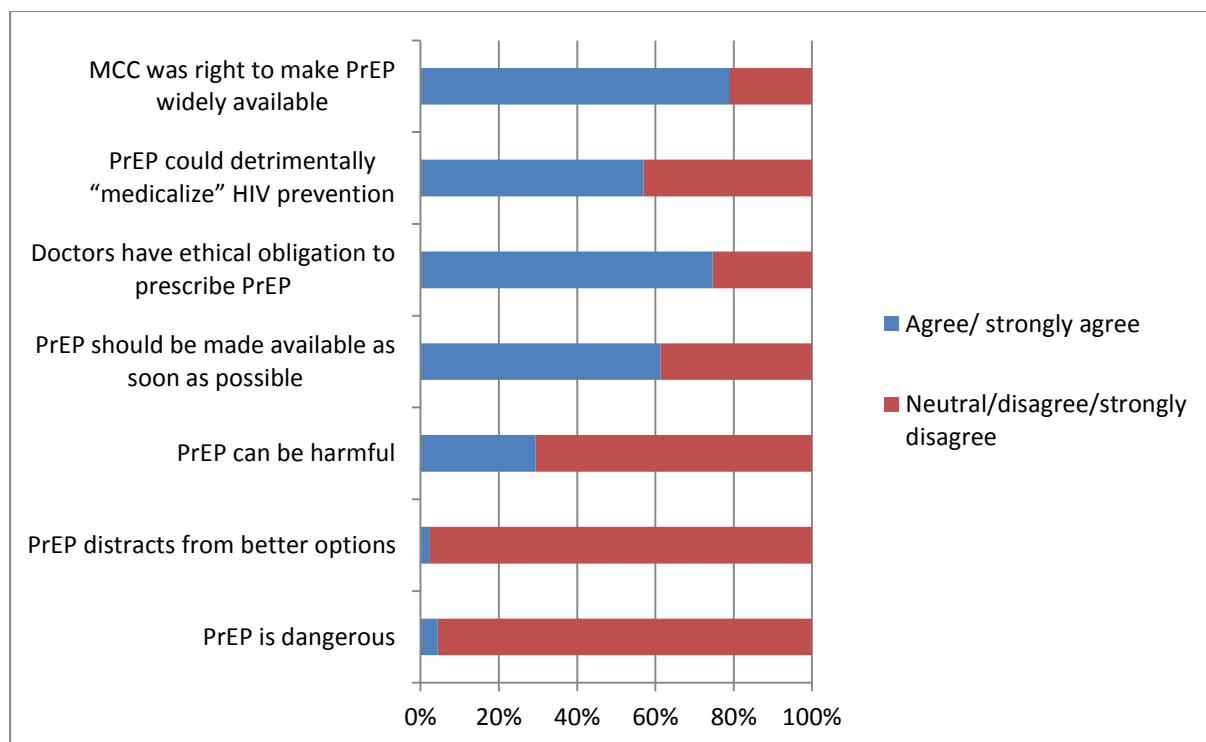
Approximately 16% of respondents felt they were very familiar with HIV PrEP in general, 74% expressed some knowledge of HIV PrEP and the results from clinical trials, and 11% expressed a lack of familiarity with Truvada being used as HIV PrEP (Table 1).

### *Statements about PrEP*

Fig 1 graphically shows the opinions responding doctors expressed regarding prescribing Truvada as PrEP.

The results are consistent with the high percentage of doctors willing to prescribe PrEP, with most doctors subscribing to the positive statements about PrEP, and very few to the negative statements, with one exception.

This was the statement that provision of PrEP may lead to the “medicalization” of HIV prevention, which 57% of the respondents endorsed.



**Fig 1: Opinions of South African doctors regarding PrEP**

### *Main hypothesis testing*

Testing of hypotheses yielded the following significant predictor variables associated with provider willingness to prescribe PrEP, as shown in Table 2:

self-identification as an expert in HIV care (OR=3.31,  $p=0.008$ ); serving at least 40% males who have sex with males (MSM) (OR=2.26,  $p=0.049$ ); being asked about PrEP by a patient (OR=2.77,  $p=0.007$ ) and rating efficacy as most important in the question asking about efficacy as a Likert scale (OR=3.29,  $p=0.000$ ).

Testing for a “purview paradox” showed no association (OR= 1.18,  $p=0.608$ ).

Table 2: Summary table of main hypothesis testing					
Question	Willing	Maybe willing/ Not willing	Odds ratio	Chi-squared	p-value
Self-identified expert in HIV care	45	6	3.31	7.14	<b>0.008</b>
Non-expert in HIV care	111	49			
>= 40% HIV positive patients	73	24	1.10	0.09	0.765
<40% HIV positive patients	83	30			
>= 40% high risk HIV negative patients	51	21	0.75	0.74	0.390
<40% high risk HIV negative patients	100	31			
>= 40% MSM	43	8	2.26	3.89	<b>0.049</b>

patients <40% MSM patients	114	48			
Being asked by patient about PrEP	68	11	2.77	7.31	<b>0.007</b>
No patients asked about PrEP	76	34			
Efficacy rated as most important concern	114	25	3.29	14.27	<b>0.000</b>
Efficacy rated 2 <sup>nd</sup> or 3 <sup>rd</sup> most important	43	31			
<b>PURVIEW PARADOX</b>					
Question	Specialist in HIV care	Non- specialist in HIV care	Odds ratio	Chi-squared	p-value
PrEP should be given in dedicated PrEP clinics	19	59	1.18	0.26	0.608
PrEP should be given by general practitioners	36	132			

### *Exploratory hypothesis testing*

Exploratory hypothesis testing, yielded the following variables associated with willingness to prescribe Truvada as PrEP, as shown in Table 3 :

At least 40% work time spent in Public Health (OR=3.21, p=0.033), knowledge about PrEP obtained from conferences (OR=4.75, p=0.000), knowledge about PrEP obtained from journals (OR=3.05, p=0.002) and from seminars (OR=2.33, p=0.018).

Associations with borderline significance included:

male sex, independent practice for at least 3 years, and resistance and disinhibition identified as most important when answering questions on a Likert scale.

### *Internal consistency of survey*

Table 3 shows an association of provider willingness with belief in patient benefit (OR= 4.34, p=0.000) and belief in the correctness of the MCC decision (OR=6.38, p=0.000).

<b>Table 3: Summary table of exploratory hypothesis testing</b>					
<b>Question</b>	<b>Willing</b>	<b>Maybe willing/ Not willing</b>	<b>Odds ratio</b>	<b>Chi-squared</b>	<b>p-value</b>
<b>Female sex</b>	82	37	0.56	3.21	<b>0.073</b>
<b>Male sex</b>	75	19			
<b>&gt;=3 Years of practise</b>	109	30	1.82	3.35	<b>0.067</b>
<b>&lt;3 years of practise</b>	46	23			
<b>&gt;=40% spent in public health</b>	31	4	3.21	-	<b>0.033*</b>



<b>&lt;40% spent in public health</b>	116	48			
<b>Knowledge about PrEP from journal</b>	67	11	3.05	9.43	<b>0.002</b>
<b>Knowledge from other sources or no previous knowledge</b>	90	45			
<b>Knowledge about PrEP from conferences</b>	57	6	4.75	12.98	<b>0.000</b>
<b>Knowledge from other sources or no previous knowledge</b>	100	50			
<b>Knowledge about PrEP from seminars</b>	61	12	2.33	5.56	<b>0.018</b>
<b>Knowledge from other sources or no previous knowledge</b>	96	44			
<b>Belief that MCC was right</b>	137	29	6.38	30.21	<b>0.000</b>
<b>Belief that MCC was incorrect</b>	20	27			
<b>Belief that patients will benefit from PrEP</b>	124	26	4.34	21.00	<b>0.000</b>
<b>Belief that patients will not benefit From PrEP</b>	33	30			
<b>Resistance rated as most important concern</b>	54	27	0.56	3.35	<b>0.067</b>
<b>Resistance rated as 2<sup>nd</sup> or 3<sup>rd</sup> most important</b>	103	29			
<b>Disinhibition most important</b>	33	18	0.56	2.81	<b>0.094</b>
<b>Disinhibition rated as 2<sup>nd</sup> or 3<sup>rd</sup> most important</b>	124	38			

<b>Adherence counselling as facilitator</b>	95	41	0.56	2.89	<b>0.089</b>
<b>Adherence counselling not an Important facilitator</b>	62	15			

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Notes:

\* Fischer's exact test used

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### *Barriers associated with prescribing PrEP*

A number of perceived barriers and concerns were asked about in questions employing a Likert scale, and the results are as below:

Mirroring the hypothesis testing results from Table 2 and Table 3, efficacy, resistance and disinhibition showed the greatest differences between those willing and those more ambivalent about prescribing PrEP in Figure 2.

Of those respondents who were willing to prescribe Truvada as PrEP, approximately 80% rated efficacy as most important, while 52% of the more unwilling doctors did so.

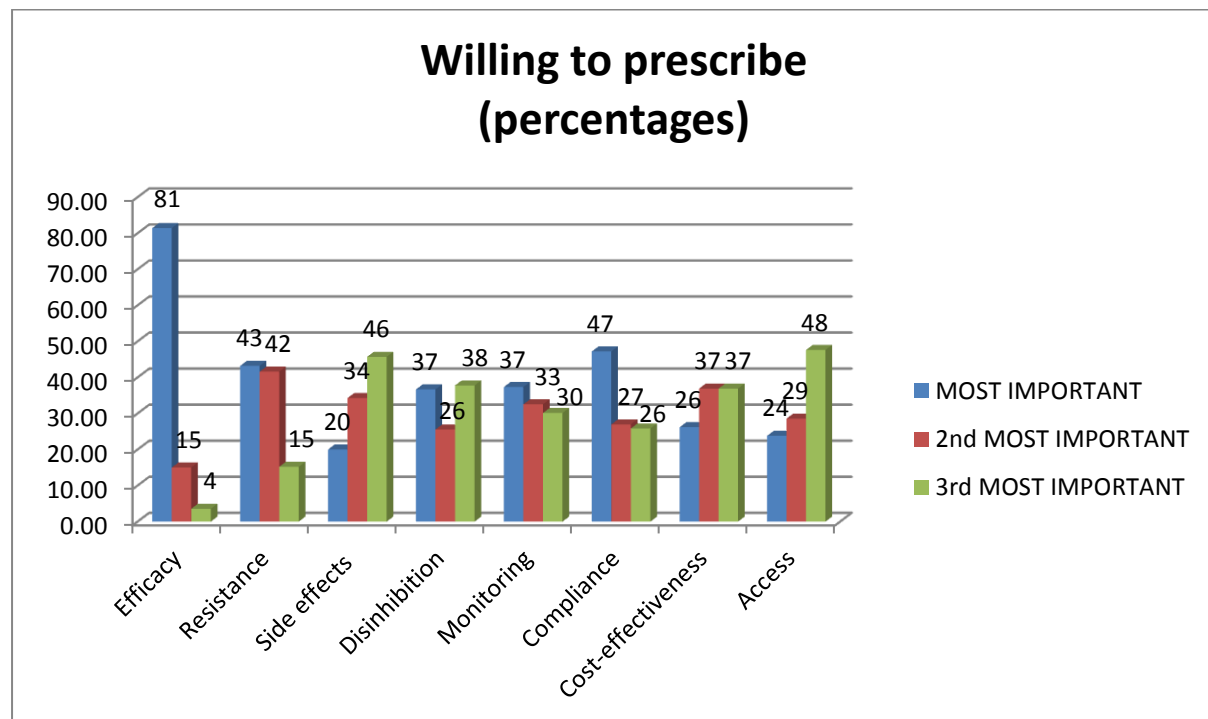
Of those willing to prescribe, 43% rated resistance as most important, while 56% of those more unwilling did so. Similarly 37% of those willing to prescribe rated disinhibition most important, while 58% of those less willing did.

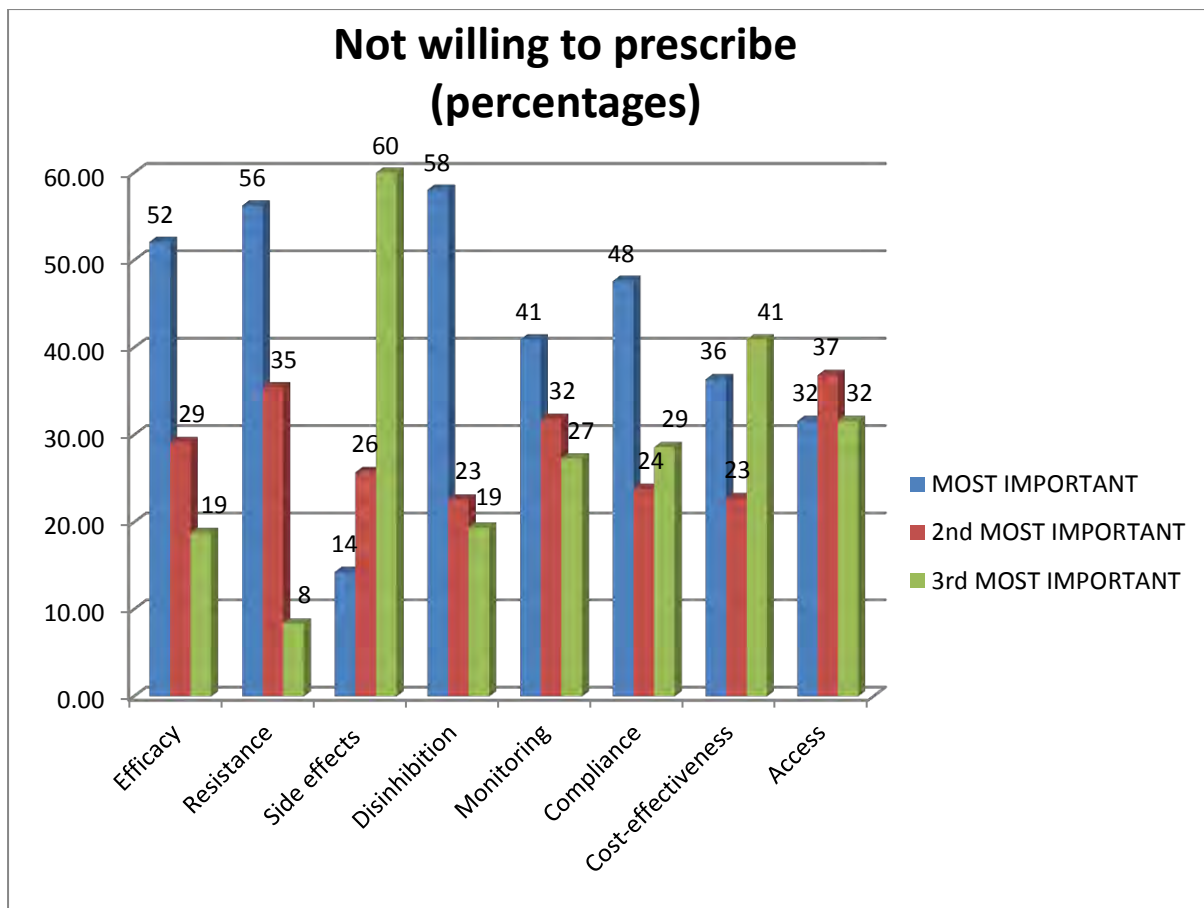
In both groups of doctors, a similar number rated side effects, monitoring for complications, and patient compliance as most important.

Other non-clinical factors were rated as most important differently in each group:

26% rated cost-effectiveness in the willing group, compared to 36% in the other group, and

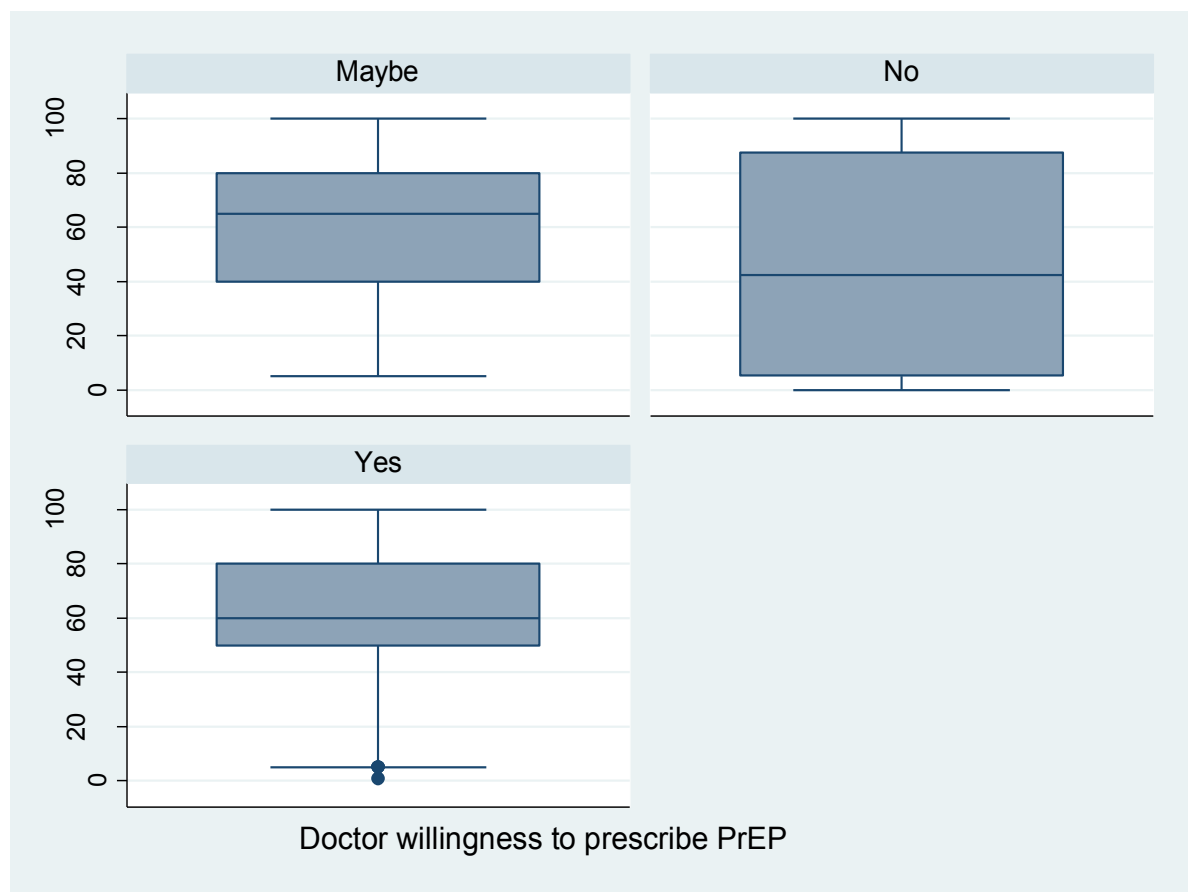
24% rated access to medication in the willing group, compared to 32% in the other group.





**Fig 2: Plot of willingness to prescribe PrEP versus perceived barriers**

Figure 3 shows the means of PrEP efficacy acceptable to doctors, with 60% minimum efficacy required by those willing and maybe willing to prescribe PrEP, and 40% minimum efficacy required in the “No” group. One-way ANOVA however revealed that this difference in means was not significant.



One-way ANOVA:

$F=0.69$ ,  $p=0.5009$

Bartlett's test for equal variances:  $\chi^2=3.3435$ ,  $p=0.188$

**Fig 3: Doctor willingness to prescribe PrEP vs efficacy desired by doctors**

### *Facilitating factors*

Exploratory hypothesis testing as in Table 3 showed no significant associations between facilitating factors shown and willingness to prescribe PrEP. However, adherence counselling

by a trained counsellor showed a borderline association with doctor willingness to prescribe PrEP (OR=0.56, p=0.089).

### *Logistic regression*

Finally a logistic regression was performed, and run on the observations for 60 participants, using a complete case analysis approach, as shown in supplemental Table 4 which shows the model building procedure using likelihood ratios (threshold p-values=0.05 for inclusion into model and p=0.1 for exclusion).

This model yielded very imprecise coefficient estimates probably due to the small sample size, and only time spent in research work and teaching both in 10% increments were significant on univariable analysis, but no variables were eventually included on multivariable analysis.

## **Discussion**

### *Factors associated with provider willingness*

The results yielded some interesting data, from which several conclusions which have clinical, and policy implications can be drawn.

This sample shows a relatively large amount of doctors willing to prescribe Truvada as PrEP, namely 157 out of 213 respondents or 74%, as shown in Table 1.

Further, previous knowledge about Truvada being approved as PrEP did not influence provider willingness to prescribe it, although it was a mediating factor in decision making on the issue.

It could also be argued that the high proportion of doctors willing to prescribe Truvada as PrEP may be due to SAMA doctors being active in subscribing to journals and attending conferences and that this active involvement resulted in them being “early adopters” of any new management regimens.

As the respondents constituted a small proportion of South African doctors, it is difficult to comment on whether the results in this preliminary survey were representative of South African doctors as a whole.

Most of the respondents were from urbanized areas such as the Western Cape, Gauteng and Kwazulu Natal. This may reflect a higher density of conferences, peer activities and greater dissemination of online and written information in urban areas, resulting in greater interest in HIV PrEP in the urbanized areas.

Hypothesis testing as in Tables 2 and 3 showed that several factors were identified as associated with provider willingness to prescribe PrEP .

These factors included previous familiarity either with PrEP or antiretrovirals, as shown by doctors rating themselves as self-identified expert in HIV care (OR=3.31, p=0.008).

Peer group learning was also confirmed as an effective mechanism to enhance decision making and willingness to prescribe Truvada for even such a novel indication, with strong associations with willingness to prescribe PrEP for obtaining knowledge from peer-reviewed journals (OR=3.05, p=0.002), conferences (OR=4.75, p=0.000) and seminars (OR=2.33, p=0.018).

Perceived patient need for PrEP by the practitioners, as shown by an association of provider willingness to being asked by a patient at least once, also played a significant role (OR= 2.77, p=0.007).

Serving patients who fell into a vulnerable group such as males who have sex with males (MSM) was as expected also positively associated with provider willingness to prescribe PrEP (OR= 2.26, p=0.049).

Surprisingly, despite the fact that 62 people in serodiscordant relationships enquired about PrEP (analysis not shown in figures), having at least 40% high risk HIV negative patients in doctors' practices was not strongly associated with provider willingness to prescribe Truvada as PrEP (OR= 0.75, p=0.390). A stronger association may, however, be more evident in future studies with a larger sample size.

#### *Purview paradox*

Unlike the result obtained by Dr Kenneth Mayer et. al[7], a "purview paradox" does not seem to exist among South African doctors, as shown in Table 2, with 132 general practitioners feeling that PrEP should be administered in any clinic, not dedicated PrEP clinics.

This may reflect the greater perception of the extent of the HIV burden in South Africa and the ethical obligation by doctors to provide means to prevent HIV.

#### *Barriers to providing PrEP*

From the hypothesis testing in Table 2, efficacy rated as most important (Question 44), was strongly associated with provider willingness to prescribe Truvada as PrEP (OR= 3.29, p= 0.000). This was also shown in Figure 3, where paradoxically 81% of doctors willing to prescribe PrEP rated efficacy as most important, versus 52% of more ambivalent providers. Interestingly enough, although one-way ANOVA did not show a significant result, Figure 3 shows a mean efficacy of 60% for Truvada as PrEP as the minimum acceptable level in those willing to prescribe PrEP versus 40% in the other group.

This is a little counter to what is expected, but may be explained by the observation that those willing to prescribe PrEP are more concerned with efficacy, but less concerned about other perceived barriers prescribing PrEP than the more ambivalent group of doctors..



For example, Table 3 shows willingness to prescribe PrEP is borderline negatively associated with concern about development of HIV resistance (OR=0.56, p=0.067) and patient disinhibition (OR=0.56, p=0.094). Also Figure 2 shows that those 43% of those doctors willing to prescribe PrEP regard development of HIV resistance as most important, versus 56% in the other group. Similarly, 37% of doctors willing to prescribe PrEP rated disinhibition as most important, versus 58% in the other group.

Issues such as monitoring of patients, concerns about patient compliance and side effects were not strongly associated with provider willingness to prescribe PrEP.

However, although not shown to be associated with willingness to provide PrEP on Table 3, so-called “efficiency” factors important to PrEP program implementation[11] may be of some concern to providers, and may negatively influence their willingness to prescribe PrEP. This is suggested in Table 1 where 57% of respondents felt that PrEP could detrimentally “medicalize” HIV prevention, and also that 49% of responding doctors felt that the patient receiving PrEP should pay for it and that only 10% were in favour of a National Health Insurance scheme in future incorporating paying for services such as PrEP provision. (data not shown on table 1).

Figure 2 also shows that 26% of those willing to prescribe PrEP rated cost-effectiveness as most important versus 36% in the more ambivalent group, and similar percentages for patient access to medication at 24% versus 32% respectively.

### *Facilitating factors*

Facilitating factors including adherence counselling by trained counsellors, nursing support and the need for continuing medical education did not affect provider willingness to prescribe PrEP, as shown in Table 3, although adherence counselling was borderline significant (OR=0.56, p=0.089) suggesting that those unwilling to prescribe PrEP were more concerned about this facilitating factor being present than the more willing group.

## **Conclusions**

### *Limitations of study*

There are several limitations to this study:

- (1) 2% of the doctors in the SAMA database (289) responded, not surprising given the facts that the survey was exclusively available online, and that only one email to reach available doctors was employed. The sample size calculation shown in the Methods section, though, yielded a total of 97 doctors needed to answer the outcome question to the required precision, so that the study was adequately powered to answer the main research question.
- (2) Non-responder bias, where doctors who did not take the survey could have differed regarding willingness to prescribe PrEP from those who did. Volunteer bias could also have played a role, as the respondents could have been early adopters of PrEP indicated by the high percentage of doctors willing to prescribe it, and could for example be more inclined to use online channels as their source of information about medical topics.
- (3) These limitations possibly influenced the generalizability of the results, making these results very much preliminary.
- (4) Social desirability bias where respondents , for example, selectively did not answer certain questions. This is suggested by the fact that 76 of the 289 survey respondents (26%) did not answer the outcome question.
- (5) Sample size leading to a lack of statistical power.

### *Suggestions for future studies*

Scope for future studies include:

- (1) Allow all doctors registered with the Health Professions Council of South Africa to participate.
- (2) Use more channels by which to reach potential respondents to a future survey, for example, journals and seminars as done by Dr Sharma et al[6]
- (3) Extending similar surveys to other health professionals, for example, nurses and counsellors
- (4) Use of qualitative studies to more closely look at the impact and valuation of factors with policy implications such as cost-effectiveness
- (5) Recently results of clinical trials involving HIV microbicide rings reported efficacy of 27% for the ASPIRE study[12], and 31% for IPM027[13]. Future surveys could ascertain doctor willingness to prescribe PrEP in this form.

Although limited in scope, this study showed willingness on the part of South African doctors to prescribe Truvada as PrEP, coupled with reasonably good awareness of the clinical aspects of prescribing PrEP and policy implications of the decision by the MCC. South African doctors seem to be willing to embrace the potential benefits and also the challenges of a new paradigm in HIV prevention.

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## **PART D: APPENDICES**

### **APPENDIX 1: SAMPLE EMAIL ADDRESSED TO DOCTORS**

To: Whom it may concern

Subject: Truvada approved for HIV prevention in addition to treatment: are you ready?

Dear Doctor

The Medicines Control Council has approved the use of Truvada (tenofovir/emtricitabine) as a means to prevent HIV in December 2015.

More specifically, the MCC has approved the use of once daily oral Truvada as HIV pre-exposure prophylaxis (PrEP) ie Truvada taken before an event that exposes the person to HIV, as opposed to post-exposure prophylaxis. This decision is based on results from clinical trials showing both efficacy and safety of Truvada used for this indication, and follows on from approval of Truvada for this indication by the Food and Drug Administration (FDA) in July 2012.

Coupled with these approvals are the release of guidelines from the Centres for Disease Control (CDC) and South African HIV Clinician Society guidelines on indications for, side effects of, and appropriate prescription of Truvada as PrEP with associated safety monitoring and counselling.

Successful implementation of these guidelines, needless to say, depends on commitment from both the patient and motivated, well informed clinicians.

This survey thus tests:

- (1) Knowledge of clinicians on HIV PrEP
- (2) Opinions or beliefs of clinicians on HIV PrEP
- (3) Concerns about prescribing HIV PrEP
- (4) Any need clinicians feel for further information on PrEP clinical trials and guidelines



The survey gives an opportunity to obtain further information on request after completion, and also the opportunity to enter a draw to win an Ipad.

At the end of the survey, a link will be provided to download the 2016 South African guidelines on use of Truvada as PrEP. A link to email Dr Llewellyn Fleurs to enter a draw to stand a chance of winning an Ipad will also be provided at the end of the survey.

It is important to note that although survey participants that send the email to enter the draw will no longer be anonymous, it will still not be possible to link your answers to you personally, in any way.

To fill in the survey, please click on the following link:

<https://www.surveymonkey.com/r/8KW3TNK>

## **APPENDIX 2: INFORMED CONSENT DOCUMENT**

### **INFORMED CONSENT DOCUMENT**

#### **LETTER OF INFORMATION REGARDING STUDY**

##### **STUDY TITLE:**

Assessing perceptions, beliefs, and readiness of doctors based in South Africa for the implementation of HIV pre-exposure prophylaxis.

##### **INVESTIGATORS:**

Linda-Gail Bekker, MBCHB FRCP PhD,

Llewellyn Fleurs, MBCHB BSc (Biochemistry).

#### **INTRODUCTION**

You are being asked to participate in a research study being conducted by a research team from the Desmond Tutu HIV Centre in Crossroads, Cape Town. Before agreeing to participate in this study, it is important that you read and understand the following explanation of the study. You are free to accept or decline participation in the study without consequence.

#### **PURPOSE OF THE STUDY**

This questionnaire has been designed to investigate physician knowledge, opinions and learning needs regarding pre-exposure prophylaxis (PrEP) for prevention of HIV infection. You do not need to have any prior knowledge of PrEP to participate in the survey.

#### **STUDY PROCEDURES**

- Participation in this study is voluntary. If you agree to participate, you will be asked to fill out this six page online questionnaire.
- This survey is confidential. Please do not include your name or any other identifying information other than what is asked in the survey.
- This survey takes about 15-20 minutes to complete and asks you questions about your knowledge and experience with PrEP, your opinions on key issues and your learning needs.
- You have the option to not answer any questions which you find confusing, uncomfortable or choose to omit for any reason.
- You also have the option to withdraw your consent by not completing the questionnaire if you so wish for any reason. If you choose to withdraw, simply exiting from the website which contains the online survey will delete all your responses and close the survey.

- All survey responses are deidentified and will remain confidential.
- Access to the online spreadsheet will be limited to the study investigators and their delegates, the Faculty of Health Sciences Human Research Ethics Committee for the purpose of monitoring the study, and the survey provider (). The results of this study may be presented by the study team at conferences, seminars or other public forums, and published in journals.
- At the end of the survey a link will be provided to download the 2016 South African guidelines on the use of Truvada as PrEP. A link to email Dr Llewellyn Fleurs to enter a draw to possibly win an Ipad will also be provided at the end of the survey.

It is important to note that although survey participants that send the email to enter the draw will no longer be anonymous, it will still not be possible to link your answers to you personally in any way.

#### POTENTIAL RISKS

There are no known risks associated with participation in this study.

#### POTENTIAL BENEFITS

Benefits to you from participating in this study may include gaining some knowledge of PrEP and issues surrounding its use. Other health care providers who serve populations at risk for HIV may also benefit from your participation in this study in the future.

#### INFORMED CONSENT

By clicking the box below, you are agreeing that you have read and understood the informed consent form and agree to participate in the study. If you require further information about this study, you may contact Prof. Linda-Gail Bekker, Principal Investigator, at (021) 406 6970 during business hours. This study has been approved by the Research Ethics Board at the University of Cape Town. If you have any questions regarding your rights as a research participant, you may contact the UCT Office of Research Ethics at 021 406 6338

*Check all that apply*

☐

I have read and understood the consent form and agree to participate in the study

**APPENDIX 3: SAMPLE INFORMATION PACK FOR DOCTORS THAT REQUEST MORE INFORMATION  
ON HIV PrEP**

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/239734564>

# Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV-1 infection

ARTICLE · SOUTHERN AFRICAN JOURNAL OF HIV MEDICINE · FEBRUARY 2015

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# Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV-1 infection



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The Southern African HIV Clinicians Society published its first set of oral pre-exposure prophylaxis (PrEP) guidelines in June 2012 for men who have sex with men (MSM) who are at risk of HIV infection. With the flurry of data that has been generated in PrEP clinical research since the first guideline, it became evident that there was a need to revise and expand the PrEP guidelines with new evidence of safety and efficacy of PrEP in several populations, including MSM, transgender persons, heterosexual men and women, HIV-serodiscordant couples and people who inject drugs. This need is particularly relevant following the World Health Organization (WHO) Consolidated Treatment Guidelines released in September 2015. These guidelines advise that PrEP is a highly effective, safe, biomedical option for HIV prevention that can be incorporated with other combination prevention strategies in Southern Africa, given the high prevalence of HIV in the region. PrEP should be tailored to populations at highest risk of HIV acquisition, whilst further data from studies in the region accrue to guide optimal deployment to realise the greatest impact regionally. PrEP may be used intermittently during periods of perceived HIV acquisition risk, rather than continually and lifelong, as is the case with antiretroviral treatment. Recognition and accurate measurement of potential risk in individuals and populations also warrants discussion, but are not extensively covered in these guidelines.

## Introduction

### Pre-exposure prophylaxis

Pre-exposure prophylaxis (PrEP) involves taking a pharmaceutical agent prior to an exposure to prevent an outcome (e.g. infection by a microbe, such as malaria). PrEP for HIV involves the use of antiretroviral (ARV) medications to prevent HIV infection. Research into the use of existing and novel PrEP agents, as well as various delivery systems, including topical gels and rings (microbicide) and oral (tablet) and long-acting injectable formulations, is ongoing.

Tenofovir (TDF) and tenofovir/emtricitabine (TDF/FTC) in a single tablet fixed-dose combination (FDC) are the oral ARV agents used in oral PrEP studies to date. The present guidelines support the use of TDF/FTC in combination for effective PrEP. TDF-containing PrEP is recommended by the World Health Organization (WHO) for people at substantial risk of HIV infection.<sup>1</sup> In December 2015, the TDF/FTC combination pill was approved for use as PrEP by the Medicine Control Council, in combination with safer sexual practices.<sup>2</sup>

The aim of this PrEP guideline is to:

- explain what PrEP is
- outline current indications for its use
- outline steps for appropriate user selection
- provide guidance to monitor and maintain PrEP users.

PrEP is indicated for HIV-negative men who have sex with men (MSM), transgender persons, heterosexual men and women (including adolescents) and people who inject drugs (PWID), who are assessed to be at high risk for HIV acquisition. PrEP should be used as part of a package of HIV prevention services (which may include regular HIV testing, condoms,

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lubrication, contraception, sexually transmitted infection (STI) management and risk reduction counselling). PrEP is also applicable to individuals at risk of HIV acquisition because they are unwilling or unable to consistently use male or female condoms, especially if in serodiscordant relationships. The user must be counselled on ongoing pregnancy and STI risk. PrEP can also be effective as part of a broader prevention package for people who use and inject drugs (PWID) in the comprehensive setting of needle and syringe exchange and opioid substitution programmes and access to ART for injecting networks. Harm reduction is an extensively proven HIV prevention intervention for PWID, but is not discussed further in these guidelines.

## Recommendations

Daily PrEP may be used intermittently during periods of perceived HIV acquisition risk, rather than continually and lifelong, as is the case with ARV treatment. HIV testing, estimation of creatinine clearance, pregnancy screening, and STI and hepatitis B screening are recommended as baseline investigations. Hepatitis B vaccination should be offered to susceptible individuals. Daily oral tenofovir/emtricitabine (TDF/FTC) as FDC, along with effective use support, can then be prescribed for eligible users. PrEP should not be given to those with abnormal renal function, nor should it be commenced in individuals with acute viral symptoms. An initial three-drug post-exposure prophylaxis (PEP) approach may be used whilst confirming HIV-negative status in an individual presenting with acute viral symptoms and a concomitant history of recent potential HIV exposure. An alternative HIV risk reduction method should be used until HIV-negative status is confirmed. Once HIV-negative status is confirmed, switching to PrEP can be discussed. Three-monthly follow-up visits to assess HIV status, pregnancy, tolerance, renal function, adherence and ongoing eligibility is recommended. Six-monthly STI screens and annual creatinine levels to estimate creatinine clearance are also recommended. Hepatitis B vaccination should be provided to susceptible clients. Headache and gastrointestinal symptoms with weight loss are relatively common although usually mild and self-limiting, occurring for the first 4–8 weeks after initiating PrEP. These can be managed with counselling support and provision of symptomatic relief. Although uncommon, ARV resistance is most likely to occur amongst those who initiate PrEP with undiagnosed acute HIV infection. There is ongoing potential for resistance development among those with sub-optimal PrEP use who become HIV-infected while on PrEP. PrEP, if taken correctly and consistently, will offer protection from HIV infection but not from other STIs or pregnancy, and clinicians should continue to support PrEP users to be aware of STI symptoms and other components of combination prevention. Research is ongoing to assess optimum dosing regimens, potential long-term effects and alternative PrEP medications. Recommendations for the use of PrEP among other at-risk individuals, and the components of these recommendations, will be informed by future evidence.

## Background

### Development of pre-exposure prophylaxis

Tenofovir disoproxil fumarate (TDF) alone or in combination with emtricitabine (FTC) was chosen for the evaluation of PrEP because of its high level of activity in inhibiting HIV replication; its acceptable safety profile; its high barrier to generating resistant virus; and its low levels of side-effects.<sup>3</sup> The protective activity of TDF and FTC has been shown in animal models, with best efficacy when both agents were used together.<sup>4,5</sup> In clinical trials, however, it has been shown that the difference in efficacy between TDF/FTC and TDF alone is insignificant. The use of TDF monotherapy for HIV prevention has not been investigated in some key populations such as MSM.

The Global iPrEx trial was the first randomised controlled trial to report decreased risk of HIV acquisition amongst at-risk MSM and transgender persons.<sup>6</sup> These findings were further confirmed in the IPERGAY and PROUD studies.<sup>7,8</sup> IPERGAY used an 'on-demand' dosing strategy. However, as yet there are no data to support such a dosing strategy in other at-risk populations, and the writing group recommends daily PrEP in all at-risk groups until further data emerge supporting 'on-demand' dosing.

The Partners PrEP and TDF2 trials were both conducted in Africa and showed high levels of protection with daily oral tenofovir-based PrEP in heterosexual men and women including those in serodiscordant couples.<sup>9,10</sup>

The Bangkok Tenofovir Study was conducted using tenofovir only as PrEP amongst PWID.<sup>11</sup> The risk overall in the study was reduced by 49%, and by up to 74% amongst those with detectable levels of tenofovir in their blood.

To date there have been 10 randomised controlled trials of TDF-based PrEP reporting HIV outcomes. The studies have involved more than 17 000 people and have demonstrated an overall reduction in HIV acquisition risk of 51% (women RR 0.57 [95% CI 0.34–0.94] and men RR 0.38 [95% CI 0.2–0.6]). Three studies in which there was high adherence to the study product (> 70% of drug detection) showed PrEP was most efficacious but HIV infection was also significantly reduced in those studies in which drug detection levels were moderate (41%–70% detection). Unfortunately in the two studies with lowest adherence (< 40% drug detection), involving heterosexual women in southern and east Africa, PrEP had no effect.<sup>12,13</sup> The reasons for the particularly low uptake and use of oral PrEP in these two studies have been speculated on elsewhere and a range of potential reasons have been suggested, including structural, behavioural and/or psychological factors. Unfortunately this has led to some controversy around the effectiveness of oral PrEP in black African women. It is important to note, however, that two of the three studies considered by the US Food and Drug Administration (FDA) prior to licensure of PrEP as a prevention modality included women from Uganda, Kenya and Botswana. What does emerge clearly from all these



studies is the fact that protection strongly correlates with adherence to the study drug, assessed in most studies by random tenofovir drug levels.

Additional open-label demonstration projects and implementation science studies amongst different at-risk populations are ongoing (<http://www.avac.org/ht/a/GetDocumentAction/1/3113>) and confirm high rates of protection amongst the individuals with best effective use. No RCTs of tenofovir-based PrEP are currently underway, although alternative ARVs, new longer-acting formulations and alternative topical applications are planned or are still in earlier phase studies (Figure 1).

## MSM, transwomen and HIV in Southern Africa

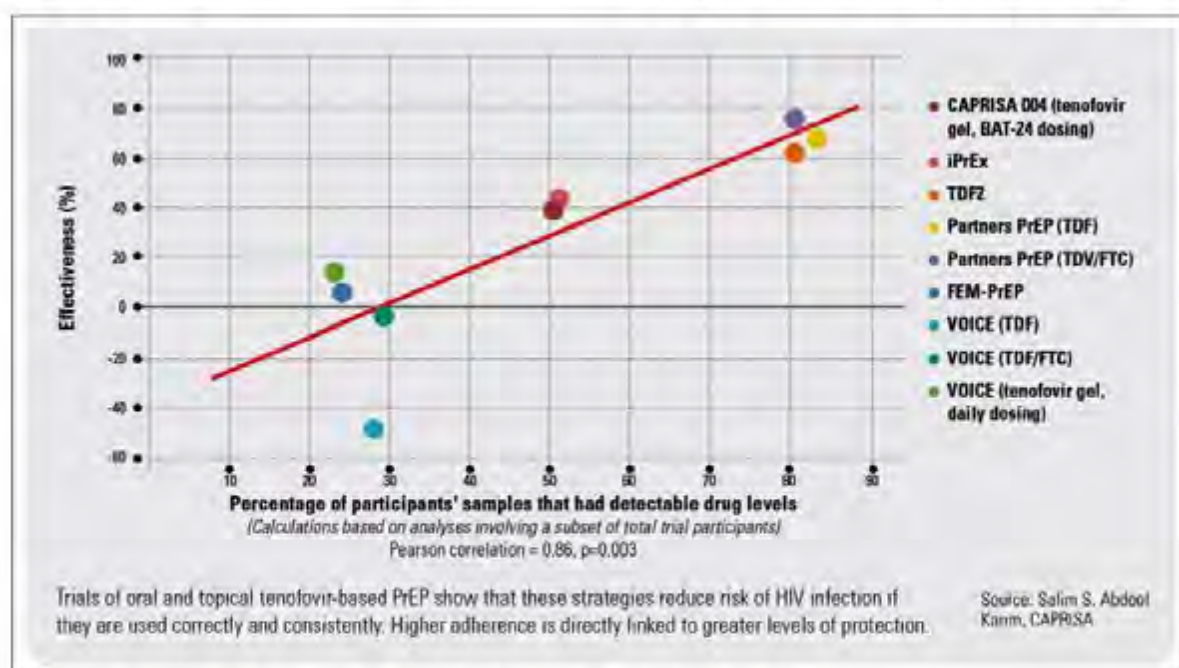
MSM is a behavioural term that describes MSM, regardless of social identity (gay, bisexual, heterosexual) or whether they also have sex with women.<sup>14</sup> MSM and transgender persons have been shown to be at disproportionately high risk of HIV acquisition and transmission.<sup>15,16</sup> Biological susceptibility (efficiency of rectal HIV transmission), behaviours (including condomless sex, anal intercourse and multiple partners) as well as structural and social factors (including homophobia and discrimination) have been associated with increased vulnerability to HIV.<sup>16</sup> Condomless receptive anal intercourse is the main risk factor for sexual transmission of HIV among MSM.<sup>17</sup> The high concentration of rectal cells vulnerable to HIV-1 infection (macrophages, T-cells and dendritic cells) and the single-cell layer of rectal mucosa, results in a per-act risk for HIV transmission that is 10–20 times greater than unprotected vaginal intercourse.<sup>17,18,19</sup>

There is emerging and consistent evidence about the high HIV burden amongst MSM in Southern Africa.<sup>20</sup> Unfortunately, little data exist on the trans populations in South Africa. HIV prevalence amongst MSM sampled in cross-sectional surveys in South Africa has ranged from 10%–50%.<sup>21,22,23,24</sup> However, owing to the lack of accurate population size estimates, it is hard to assess attributable risk.<sup>25</sup> A 2009 modelling study on the modes of HIV transmission in South Africa estimated that 8% of all new HIV infections in South Africa occur among MSM.<sup>26</sup> High-risk sexual practices (including unprotected anal intercourse, multiple and concurrent partnerships, and sex work) and limited knowledge about HIV and substance use (alcohol, methamphetamines and heroin) have been associated with increased risk for HIV infection amongst MSM in South Africa.<sup>15,22,23,24,27,28,29</sup>

Many MSM also have female sexual partners. Almost half (49%) of the participants in a Soweto-based MSM study reported recent female sexual partners.<sup>23</sup> Homophobia, stigma and discrimination (including criminalisation of same-sex behaviours in some Southern African countries), healthcare worker ignorance (about MSM and transgender vulnerability to HIV and appropriate management of MSM clients) and the heterosexual focus of the HIV response have been contributing factors to the failure of Southern African public health services to address the health needs of MSM and transgender persons.<sup>15,20,30,31,32,33,34,35,36,37</sup>

## Motivation for a pre-exposure prophylaxis guideline

The initial iPrEx trial results contributed to an earlier version of these guidelines and the development of interim guidance



Source: AVAC Report 2015: Research & Reality; [http://www.avac.org/sites/default/files/infographics/PrEP\\_by\\_Numbers\\_jan2016.jpeg](http://www.avac.org/sites/default/files/infographics/PrEP_by_Numbers_jan2016.jpeg)

FIGURE 1: Effectiveness and adherence in trials of oral and topical tenofovir-based prevention.

on the use of PrEP amongst MSM by the United States Centers for Disease Control and Prevention.<sup>28</sup> These revised guidelines include all at-risk populations consistent with all accrued clinical evidence, the CDC guidelines<sup>29</sup> and recent (2015) WHO recommendations.<sup>1</sup> Southern African guidelines will assist practitioners who may be considering, or are already, prescribing PrEP to people at risk.

### Identification of potential pre-exposure prophylaxis users

Providers should educate and counsel potential PrEP users about PrEP and conduct an individualised risk-benefit assessment to assess eligibility (Box 1). The eligibility assessment requires that providers have developed sufficient client rapport to effectively assess risk based on these self-reported behaviours.

### Indications for the use of pre-exposure prophylaxis

PrEP should be considered for people who are HIV-negative and at significant risk of acquiring HIV infection (see Boxes 2 and 3). PrEP may be suitable for:

- any sexually active HIV-negative MSM or transgender person who wants PrEP
  - those with HIV-positive sexual partner(s) who are not confirmed virologically suppressed
  - partner(s) of unknown HIV status
  - recent STI
  - multiple sexual partners
  - history of inconsistent or no condom use
  - commercial sex work
  - recurrent PEP users
  - history of sex whilst under the influence of alcohol or recreational drugs
- heterosexual women and men who want PrEP, targeting especially
  - those with HIV-positive sexual partner(s) who are not confirmed virologically suppressed
  - partner(s) of unknown HIV status
  - recent STI
  - multiple sexual partners
  - history of inconsistent or no condom use
  - commercial sex work

BOX 1: Risk behaviour assessment for sexual HIV acquisition.

<p><b>Risk behaviour assessment for MSM and transwomen</b> In the past 6 months:</p> <ol style="list-style-type: none"> <li>1. Have you had sex with men, women or both?</li> <li>2. How many men have you had sex with?</li> <li>3. How many times did you have receptive anal sex with a man who was not wearing a condom?</li> <li>4. How many of your partners were HIV-positive or of unknown HIV status?</li> <li>5. With these positive/unknown status partners, how many times did you have insertive anal sex without wearing a condom?</li> </ol> <p><b>Risk behaviour assessment for heterosexual men and women</b> In the past 6 months:</p> <ol style="list-style-type: none"> <li>1. Have you had sex with men, women or both?</li> <li>2. How many men/women have you had sex with?</li> <li>3. How many times did you have vaginal or anal sex when neither you nor your partner wore a condom?</li> <li>4. How many of your partners were HIV-positive or of unknown HIV status?</li> <li>5. With these positive/unknown status partners, how many times did you have vaginal or anal sex without wearing a condom?</li> </ol>
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Source: Adapted from HHS guideline (Pre-exposure prophylaxis for the prevention of HIV infection in the United States – 2014 clinical practice guideline)

- serodiscordant couples trying to conceive
- recurrent PEP users
- history of sex whilst under the influence of alcohol or recreational drugs
- people who inject drugs
  - HIV-negative PWID with HIV-positive/unknown status injecting partner(s)
  - share injecting needles and drug preparation equipment
- all of the above groups include adolescents and sex workers, which each constitute special groups meriting specific consideration
  - especially vulnerable are young MSM and adolescent girls.

PrEP should be provided as part of a combination prevention package.

### Contraindications to pre-exposure prophylaxis

- HIV-1 infected or evidence of possible acute infection
- suspicion that patient might be in the window period for HIV testing following potential exposure
- adolescents < 35 kg or < 15 years of age who are not Tanner stage 3 or greater should not be given TDF

BOX 2: Indications for the use of pre-exposure prophylaxis.

<p>1. Any sexually active HIV-negative MSM or transgender person especially:</p> <ul style="list-style-type: none"> <li>▪ those with HIV-positive sexual partner(s) who are not confirmed virologically suppressed</li> <li>▪ partner(s) of unknown HIV status</li> <li>▪ recent STI</li> <li>▪ multiple sexual partners</li> <li>▪ history of inconsistent or no condom use</li> <li>▪ commercial sex work</li> <li>▪ recurrent PEP users</li> <li>▪ history of sex whilst under the influence of alcohol or recreational drugs</li> </ul>
<p>2. Heterosexual women and men especially:</p> <ul style="list-style-type: none"> <li>▪ those with HIV-positive sexual partner(s) who are not confirmed virologically suppressed</li> <li>▪ partner(s) of unknown HIV status</li> <li>▪ recent STI</li> <li>▪ multiple sexual partners</li> <li>▪ history of inconsistent or no condom use</li> <li>▪ commercial sex work</li> <li>▪ serodiscordant couples trying to conceive</li> <li>▪ recurrent PEP users</li> <li>▪ history of sex whilst under the influence of alcohol or recreational drugs</li> </ul>
<p>3. People who inject drugs:</p> <ul style="list-style-type: none"> <li>▪ HIV-negative PWID with HIV-positive/unknown status injecting partner(s)</li> <li>▪ share injecting needles and drug preparation equipment</li> </ul>
<p>4. All of the above groups include adolescents and sex workers, which each constitute special groups meriting specific consideration:</p> <ul style="list-style-type: none"> <li>▪ Especially vulnerable are young MSM and adolescent girls.</li> </ul>

BOX 3: Eligibility criteria for pre-exposure prophylaxis use.

<p><b>Eligibility criteria for PrEP use include:</b></p> <ul style="list-style-type: none"> <li>• anyone identified by the provider and client as being at high risk for HIV exposure (see text box on indications for the use of PrEP)</li> <li>• no contraindications to FTC/TDF FDC</li> <li>• HIV-negative by routine rapid antibody test and not thought to be in the window period for HIV seroconversion</li> <li>• absence of symptoms of acute HIV infection (recent acute viral illness) and, if symptoms reported, HIV-negative by 4th-generation HIV test or other HIV antigen test if available (this reduces, but doesn't eliminate, the window period)</li> <li>• willing and able to attend 3-monthly PrEP maintenance visits, inclusive of HIV counselling and testing, clinical review and safety monitoring procedures</li> <li>• client understanding that the protection provided by PrEP is not complete, and does not prevent other STIs or unwanted pregnancies, and therefore PrEP should be used as part of a package of HIV prevention services (inclusive of condoms, lubrication, contraception, risk reduction counselling and STI management)</li> <li>• recurrent use of PEP.</li> </ul>
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- poor renal function (estimated creatinine clearance < 60 mL/min)
- TDF should not be co-administered with other nephrotoxic drugs, for example, aminoglycosides
- unwilling or unable to return for 3-monthly HIV testing, counselling and safety monitoring visits
- pregnant or breastfeeding women<sup>2</sup> (see section below entitled Special clinical considerations).

## Initiation of pre-exposure prophylaxis

Steps for the screening/baseline visit, PrEP initiation visit and maintenance of PrEP are described below.

### Baseline investigations

After documenting eligibility and motivation for PrEP use, mandatory baseline investigations should be completed (Table 1). The minimum package of tests offered should include:

- assessment of HIV status: Preferably use laboratory ELISA. If not available, use a fourth generation rapid test. Always repeat a positive test with a confirmatory test. If a fourth generation test is not available, defer PrEP commencement, use rapid test available in facility and repeat in 2–4 weeks whilst counselling client on risk reduction. If this subsequent test is negative and there is no reported recent risk and no symptoms, PrEP may be initiated
- where history of recent exposure, consider PEP per guidelines before initiating PrEP
- check creatinine and calculate creatinine clearance
- syndromic STI screen or, if resources allow, a full STI panel regardless of symptoms. Treat any STIs detected as appropriate, according to the relevant local guidelines
- hepatitis B surface antigen and antibody – if both negative, vaccinate against hepatitis B virus (HBV). Acute or chronic HBV is not a contraindication to PrEP but monitoring of LFTs is advised, especially if considering cycling off PrEP
- pregnancy screen.

Condoms and condom-compatible lubrication should be provided, and arrangements made for follow-up.

TABLE 1: Mandatory baseline investigations for pre-exposure prophylaxis initiation.

Screening	Method
HIV infection	Laboratory ELISA preferably – fourth generation rapid if ELISA not available
Renal function	eGFR > 60 mL/min
Hepatitis B screen	Surface antigen (HBsAg) Antibody to surface antigen (HBsAb)
STI screen	Symptomatic screen Examination if indicated Urine dipstick for urethritis Serological screening for syphilis (rapid or laboratory) Full STI panel if resources allow
Pregnancy screen	Rapid pregnancy test or beta HCG

### Problems with using rapid HIV tests in the field

There are several point of care (POC) or rapid tests available for detection of HIV in the field. Rapid and accurate diagnosis of HIV is needed in the setting of PrEP. This on-site detection of HIV removes the risk of loss to follow-up and decreases the time of individuals taking PrEP if they are HIV-positive. A major downfall of POC HIV diagnostic tests is that they have a larger window period for HIV diagnosis at PrEP commencement than molecular-based assays and are also more prone to inaccurate reporting. There is a growing need to ensure that optimal conditions for rapid HIV testing are followed, ensuring that the highest level of quality and sensitivity is achieved.<sup>40</sup> This includes improved training of both technical and clinical staff; improvement of testing space in the clinic; improvement of laboratory information systems for management of the patient results; and the need to implement external quality programmes covering all steps of the assay.

### Implementing pre-exposure prophylaxis

The PrEP initiation visit should take place no longer than one month after the screening/baseline visit. At this visit, review lab ELISA results, repeat the rapid HIV test and do a review for acute viral symptoms. Review results from baseline investigations and confirm that estimated creatinine clearance is > 60 mL/min. Commence HBV vaccination if susceptible and provide STI treatment as required (refer to latest national guidelines). Educate the user about potential PrEP side-effects and their management, as well as signs and symptoms of acute HIV infection (and the need to return for urgent HIV testing). HIV testing should be repeated every 3 months.

Initiate an effective PrEP use plan (Box 4) and provide a one-month TDF/FTC 300/200 mg (FDC) prescription (one tablet orally daily) together with a one-month follow-up date (Table 2). Those individuals with a recent high-risk exposure (e.g. a sex worker) can transition from PEP to PrEP.

It is important to bear in mind that MSM initiating PrEP need 7 days of daily dosing to reach adequate anal/rectal tissue levels, whilst women need up to 20 days of daily dosing to achieve protective vaginal tissue levels of PrEP drugs. During this period, other protective precautions must be used, such as abstinence or condoms. This should also be borne in mind in users who stop and start PrEP according to their periods of risk. PrEP medications should be continued for 28 days after the last potential HIV exposure in those wanting to cycle off PrEP.

BOX 4: What if users ask about stopping condom use while on pre-exposure prophylaxis?

1. Do not be judgemental about patient preferences.
2. Explain that this is a valid choice but there are potentially negative consequences.
3. Stress that PrEP prevents HIV but not STIs.
4. Stress that PrEP prevents HIV but not pregnancy.
5. Confirm a regular STI screening and management plan.
6. Confirm an effective and acceptable contraception plan where indicated.
7. Vaccinate against all vaccine-preventable STIs, e.g. hepatitis A and B and HPV where possible.

TABLE 2: Summary of pre-exposure prophylaxis visits and procedures.

Visit	Recommended procedures
Screening	Educate about the risks and benefits of PrEP Assess risk and eligibility Conduct HIV counselling and testing, serum creatinine level, hepatitis B and STI screen, pregnancy test Contraceptive counselling and offer services Arrange follow-up visit
PrEP initiation	Conduct HIV counselling and testing Confirm eligibility (including investigation results and creatinine clearance calculation) Commence hepatitis B vaccination if indicated Provide STI treatment if indicated Pregnancy test Educate client about PrEP side-effects and management Educate client about signs and symptoms of acute HIV infection Discuss behaviours that promote bone health, such as weight-bearing exercise and avoiding alcohol, tobacco and recreational drugs Initiate a medication effective use plan Provide condoms and lubricant Contraceptive counselling and offer services as appropriate Provide one-month TDF/FTC (FDC) prescription and follow-up date
One-month follow-up	PrEP initiation visit, PLUS: • Assess tolerability, side-effects and effective use • Actively manage side-effects • Measure serum creatinine and calculate creatinine clearance • Contraceptive services • Provide three-month TDF/FTC (FDC) prescription and follow-up date
Four-month follow-up and 3-monthly maintenance visits	Repeat procedures done at one-month follow-up Measure serum creatinine and calculate creatinine clearance at four-month follow-up, and 12-monthly thereafter Conduct 6-monthly STI screen, including urine dipstick and rapid syphilis test Complete hepatitis B immunisation at 6 months

FDC, fixed-dose combination; FTC, emtricitabine; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; TDF, Tenofovir.

## Risk reduction counselling

Risk-reduction counselling is a behavioural intervention that attempts to decrease an individual's chances of acquiring HIV and other STIs,<sup>41</sup> and should be implemented together with effective use counselling and contraceptive counselling at follow-up visits for PrEP users. The main objective of risk-reduction counselling is for clients to set a realistic goal for behaviour change that could reduce their risk of contracting HIV. This is most effective when it is non-prejudicial and user-centred. Risk reduction counselling can be provided by any trained healthcare provider and should address the following points:

- explore the context of the user's specific sexual practices, and assist in recognising which of their behaviours are associated with higher risk of HIV infection. Clinicians should also be aware that clients might not always perceive their own risk, or may be in denial about it
- identify the sexual health protection needs of the user and reflect on what their main concerns appear to be
- strategise with the user on how they can manage these concerns or needs
- agree on which strategies the user is willing to explore, and guide the user to decide on how to implement the strategy (Box 4).

For effective use support, see Box 5.

Adherence to daily PrEP medication, as shown in the iPrEx study and other PrEP trials, is a challenge. Effective use

### BOX 5: 'Adherence' versus 'effective use'

These guidelines use the term 'effective use' rather than 'adherence'. Adherence is often understood by healthcare workers, especially when applied to ARV treatment adherence, as life-long and at correct dosing intervals to ensure viral suppression. Oral PrEP must be taken, ideally daily, during times of HIV exposure risk, although there are some data suggesting that less than perfect adherence is still highly effective in MSM. There may be times when it would be appropriate to cycle off oral PrEP, for example when MSM move out of 'seasons of risk', or when female sex workers (FSW) return home to visit family, taking a break from sexual activity. If appropriate consistent use of oral PrEP is measured with the same standard as we measure ARV treatment adherence, it may show up as lacking, when in fact the population at risk has used the drug effectively. The term 'effective use' is preferred to when discussing whether ARV-based prevention has been used successfully; this is akin to 'effective use of condoms' as we seldom talk about condom adherence.

counselling should be implemented at each visit where PrEP prescriptions or distributions are made. In iPrEx, participants who took PrEP more consistently and had evidence of drug detection in their blood, had higher levels of protection than those who did not.<sup>3</sup> These findings have been duplicated in other PrEP studies in different study populations. Users will need to be made aware of the fact that drugs only work if present at adequate levels in tissues and, preferably, that drug levels should be adequate before and after exposure to HIV has occurred. The use of cellphone reminders, pillboxes, and linking pill taking with a daily routine activity are currently being evaluated for their impact on improving PrEP effective use. Clinicians and clients could use any of these or other strategies to assist in maximising effective use (see Box 6 on tips to support effective use). Any trained healthcare worker can implement effective use counselling. A client-centred approach is recommended. Drug level testing for tenofovir levels in plasma is available, but is expensive. Drug level testing may be useful to assess effective use in the future.



**BOX 6: Tips to support effective use.**

Include user-focused effective use counselling at each contact. Provide a clear explanation of the benefits of effective use. In a neutral manner, ask if the user has any challenges that may make taking PrEP difficult. Also explore possible facilitators to pill taking. Include identified facilitators when developing strategies to improve effective use of PrEP.<sup>43</sup>

**Options to improve daily pill taking:**

- Use reminders (cellphone, alarm clock, diary, partner reminder).
- Link with daily activity (breakfast, brushing teeth).
- Use a pillbox.
- Food is NOT required for pill taking.
- Join an on-line support group, e.g. Facebook: PrEP Rethinking HIV Prevention or #wethebrave.

**Managing abnormal screening results**

Clients with abnormal renal function (estimated creatinine clearance < 60 mL/min) should not be placed on PrEP. An abnormal estimated creatinine clearance result could be rechecked after 2 weeks and, if renal function returns to normal and other PrEP eligibility criteria are met, PrEP may be initiated. Those who are susceptible to hepatitis B should be immunised. Clients with acute or chronic hepatitis B can be safely initiated onto PrEP but may require LFT monitoring.<sup>44</sup> Clients with a history of pathological bone fracture, a family history of osteoporosis, or decreased bone mineral density on DEXA scanning, should be educated on ways to improve bone health, such as weight-bearing exercise and avoiding alcohol, tobacco and recreational drugs.<sup>45</sup> Clients who are ineligible for PrEP require support to access other prevention options (see HIV Prevention text box). Treat STIs syndromically as per national guidelines.<sup>46</sup> Consider empiric gonorrhoea and chlamydia treatment for MSM who are highly sexually active, even in the absence of symptoms (especially where STI laboratory screening is not feasible). Most MSM with gonorrhoea and chlamydial infection are more likely to be asymptomatic than symptomatic,<sup>45,46</sup> and can be managed in line with STI treatment guidelines (refer to latest national guidelines).

**Safety monitoring and maintenance**

PrEP users require an initial one-month follow-up to assess ongoing eligibility, tolerance, safety and effective use. Hepatitis B vaccination and STI treatment (as appropriate), condoms and condom-compatible lubricant, contraceptive services, risk reduction counselling, effective use support, a 3-month prescription for TDF/FTC FDC and a follow-up date should be provided at this visit. Thereafter, 3-monthly visits are recommended (Table 3). Check the creatinine at the first-month and fourth-month visits, and thereafter 12-monthly. Check rapid HIV every 3 months.

Each visit should be viewed as an opportunity for counselling and risk assessment. Discuss with the user at each visit whether PrEP is still needed. Emphasise the importance of effective use of PrEP to gain maximum ongoing benefit from PrEP.

**TABLE 3: Hepatitis B immune status and pre-exposure prophylaxis eligibility.**

Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (HBsAb)	Action
Negative (-)	Negative (-)	Start PrEP, vaccinate concurrently
Negative (-)	Positive (+)	Start PrEP, no vaccine needed
Positive (+)	N/A	Refer for evaluation

N/A, not applicable; PrEP, pre-exposure prophylaxis.

By mutual agreement, PrEP should be stopped if: HIV test is positive; the client no longer meets eligibility criteria; the client does not need PrEP; the client feels that adherence to PrEP is too onerous; or it is perceived by the clinician that the risks of PrEP outweigh potential benefits. Users who are ineligible for PrEP require support to access other prevention options (see HIV prevention text box).

PrEP users should be reminded that PrEP is not conceptualised as a life-long therapy. It should be used while there is risk of sexual or other exposure to HIV. PrEP users are therefore expected to cycle on and off PrEP as dictated by their current level of sexual risk. A reminder should be given that, if restarting PrEP, adequate protection only occurs after 7 days of dosing for anal sex and 20 days of dosing for vaginal sex or needle risk in PWID. HIV-negative status should be confirmed before restarting PrEP. If stopping PrEP, medication should be taken for 28 days after the last potential exposure to HIV.

**Managing abnormal follow up visit results**

PrEP should be stopped if estimated creatinine clearance < 60 mL/min. Repeat creatinine clearance should be rechecked after 2 weeks; if renal function returns to normal and other PrEP criteria are met, PrEP may be restarted. STIs should be treated syndromically (refer to latest national guidelines).

**Risks and side-effects****Antiretroviral resistance**

At the time of writing the guideline, the only HIV resistance documented to date amongst PrEP users has been amongst clients who initiated PrEP when they were already HIV infected (during acute HIV infection). Predictably, the FTC resistance mutation M184V was the first to occur.<sup>3</sup> To prevent the risks of developing ARV resistance, clinicians must focus on not commencing or reinitiating PrEP after a break, during acute HIV infection (Box 7).

HIV testing should be done 3-monthly, and should be accompanied by an HIV exposure assessment, symptom screen and a targeted examination to exclude acute HIV infection (Box 8). HIV testing should also be repeated whenever symptoms of a viral illness are present. Clinicians should advise clients on the need for an HIV test before resuming PrEP if it was stopped, particularly if they have potentially been exposed to HIV during this period.

**Side-effects**

There is a large TDF/FTC FDC safety database derived from millions of HIV-positive individuals receiving ART.<sup>8</sup> In addition, the 17 000 individuals exposed during the clinical trials and an increasing number of individuals in demonstration projects confirm the extremely good safety profile of TDF/FTC FDC use in HIV-negative individuals.<sup>8</sup>

**BOX 7: Strategies to reduce the likelihood of antiretroviral resistance.****Feasibly exclude acute HIV infection before initiating PrEP by:**

- conducting antibody HIV testing before commencing or re-prescribing PrEP
- enquiring about pill taking patterns and whether any pills were missed
- among persons with a negative HIV antibody test, conducting a clinical screen to detect signs and symptoms of acute HIV infection – history of fever, sore throat, rash, joint pain, cough in the past month and a targeted examination (temperature, ENT and skin exam) (see Acute HIV infection text box)
- considering time period between last potential HIV exposure and window period of tests being used
- If symptoms or signs of acute HIV infection found:
  - At screening: postpone PrEP until symptoms subside and rapid antibody test remains negative at 2–4 weeks' follow-up
  - At screening: do not initiate PrEP until follow-up HIV antigen/antibody testing (2–4 weeks) complete
  - At follow-up: may elect to continue PrEP while awaiting results of follow-up HIV antigen/antibody testing (2–4 weeks) or may decide to withhold PrEP until follow-up tests available
- Note that, if PrEP has been taken consistently, breakthrough infection is unlikely. Withholding PrEP may put an effective user at greater risk for HIV acquisition
- Support client to maximise effective use and include effective use counselling at each visit
- Stop PrEP should requirements for PrEP eligibility not be fulfilled or if client recognises risk profile has altered or wishes to use a different combination of prevention
- Counsel client that recommencement will require all of the above steps again

**BOX 8: Acute HIV infection.**

Severity of the syndrome ranges from mild non-specific 'viral' or 'flu-like' symptoms to a severe infectious mononucleosis-like illness with immune dysregulation and transient profound CD4 depletion.<sup>49,50</sup>

**Symptoms:**

- malaise
- anorexia
- myalgias
- headache
- sore throat
- sore glands
- rash.

**Signs:**

- fever, sweating
- generalised lymphadenopathy
- hepatosplenomegaly
- non-exudative pharyngitis
- orogenital herpetic ulceration
- truncal rash (maculopapular or urticarial)
- viral meningitis
- Guillain-Barre syndrome
- pneumocystis pneumonia†
- cryptococcal meningitis†
- oral/oesophageal candidiasis.

†, Extremely rare.

The major toxicities associated with TDF/FTC have been extremely rare in PrEP exposure to date. Minor side-effects have been relatively common, but mild and self-limiting (approximately 1 in 10 individuals in the first 1–2 months).

**Gastrointestinal side-effects**

The side-effects related to TDF/FTC FDC use in PrEP trials (nausea, weight loss) were mostly self-limiting mild start-up symptoms (first month), but these may adversely affect persistent PrEP effective use. Supportive counselling and symptomatic treatment (anti-emetics) of these symptoms is often sufficient to assist the user to persist beyond the first month, after which the symptoms tend to subside. This may also be accompanied by mild headache and some malaise. Rates of other GIT symptoms (bloating, abdominal tenderness, flatulence) amongst PrEP trial participants who took TDF/FTC FDC were not significantly different from those who took placebo.<sup>6</sup>

**Renal toxicity**

Modest, transient increases in serum creatinine have been noted in completed PrEP studies, but these did not persist after stopping PrEP nor recur on rechallenge. Proteinuria, decreasing glomerular filtration rate (GFR) and Fanconi's syndrome have been described in the setting of ART, and decreased GFR has been described in the setting of PrEP but has not caused clinical harm.<sup>6</sup> Renal function needs to be measured prior to commencement and monitored in clients using PrEP by measuring serum creatinine and calculating the estimated creatinine clearance. These parameters should be measured at baseline, at month 1, month 4 and then annually thereafter. Hypertensives, diabetics and those with existing glomerulonephropathies (if the benefit of PrEP is still deemed to outweigh clinical risk) should be monitored more frequently. TDF/FTC FDC-based PrEP should be avoided in patients who require the use of other nephrotoxic drugs, such as aminoglycosides for the treatment of drug-resistant tuberculosis (TB). Clients with creatinine clearance < 60 mL/min should not be placed on PrEP and, if found during maintenance, PrEP should be discontinued.

**Decreased bone mineral density**

Decreases in bone mineral density associated with TDF and FTC/TDF FDC have been observed in completed PrEP trials. Decreases were less than those observed in HIV-infected individuals treated with the same drugs, and appeared to stabilise over time.<sup>49,50</sup> No difference in fracture rates was seen. Recreational drugs (amphetamines and inhalant use) were associated with reductions in bone mineral density in HIV-negative MSM taking TDF, suggesting some synergistic impact.

**Hepatitis B management**

TDF and FTC both have hepatitis B antiviral activity. The potential risk exists that exposure to these antivirals may treat unidentified chronic hepatitis B infection, with a consequent viral flare (rebound) upon drug withdrawal that can result in severe liver injury.<sup>51</sup> This phenomenon has not been described with PrEP use to date. However, it is recommended that screening for hepatitis B surface antigen and antibodies occurs prior to PrEP commencement.

If it is recommended that, if hepatitis B surface antigen (HBsAg) is positive, the client be investigated prior to commencement of short-term PrEP (Table 3). PrEP is not contra-indicated in those with HBV but we recommend that additional liver function monitoring should be performed. PrEP users with persistently elevated or abnormal liver function tests should be referred for assessment. A possible approach to those with chronic hepatitis B infection may be to prescribe long-term TDF/FTC FDC. Liver function tests should be checked after stopping PrEP in those with chronic hepatitis B infection. Users who are negative for both HBsAg and hepatitis B surface antibody (HBsAb) should commence a hepatitis B vaccine schedule. People with chronic hepatitis B infection



may choose to continue using TDF and FTC to control their hepatitis, even if they do not require these drugs any longer for the indication of PrEP. Users with a history of injecting drug use should be screened for hepatitis C and, if positive, referred for further care.

### Other side-effects

Hyperpigmentation may occur as a side-effect to FTC. The clinician should explain that this is not harmful. Lamivudine (3TC) can be substituted but this will increase the pill burden, which may have an impact on effective PrEP use. PrEP studies to date have used either TDF or TDF in combination with FTC, rather than 3TC.

### Risk compensation

This term refers to the theoretical risk that individuals commencing PrEP will neglect other safer-sex measures, and put themselves at increased risk of HIV exposure. To date, evidence of this has not been borne out in PrEP trials. It may be, however, that during counselling it is apparent that a client may not be able to or simply cannot use condoms or other safer-sex modalities. In these cases, PrEP if used consistently during HIV exposure may significantly reduce HIV infection. Providers should gauge this during risk reduction and effective use counselling opportunities.

## HIV prevention package for pre-exposure prophylaxis users

The prevention of HIV acquisition requires a comprehensive approach, inclusive of a combination of biomedical and behavioural/psychosocial interventions tailored to individual needs. Where feasible, condoms and condom-compatible lubrication are key components of all HIV prevention packages, supported by contraceptive services, STI detection and treatment, appropriate use of ART (PEP), and counselling around the identification of high-risk practices and ways to circumvent or reduce risk. Individuals should be encouraged to understand what each component of the prevention package offers and, together with the provider, should devise the optimal package for their own lifestyle.

## Stopping pre-exposure prophylaxis

PrEP should be stopped: (1) whenever an HIV test is positive, (2) at client request, (3) for safety concerns (particularly if creatinine clearance < 60 mL/min) and (4) if the risks of PrEP outweigh the potential benefits. Ongoing linkage to appropriate HIV prevention services and contraceptive services should be encouraged, as well as the use of other HIV prevention strategies, as needed.

The duration of PrEP use may vary and individuals are likely to start and stop PrEP depending on their risk assessment at different periods in their lives – including changes in relationship status, behaviours and ability to adhere to a PrEP maintenance programme. Clients should be advised

that an HIV test at minimum should be done before PrEP is recommenced. Clinicians may want to discuss the options of when to discontinue PrEP with their clients.

## Other notes for pre-exposure prophylaxis prescribers

### Pre-exposure prophylaxis will not suit all users

PrEP should be considered for clients who are most likely to benefit from this specific prevention strategy, ideally as part of a package of HIV prevention services (Box 9).

### Pre-exposure prophylaxis usage requires commitment

Usage will require commitment from both the provider and the user to ensure success. Providers may need to be innovative in providing support to PrEP users and also find ways to make participation in a PrEP programme as easy and convenient as possible. This requires ensuring that structural, logistical barriers are minimised as much as possible and that participants are provided with an encouraging and positive approach from providers.

## Special clinical considerations

### Women who become pregnant or breastfeed on pre-exposure prophylaxis

HIV-negative women in serodiscordant relationships are at risk of acquiring HIV infection whilst trying to conceive through unprotected sex. Pregnancy itself is also associated with an increased risk of becoming infected with HIV. The use of PrEP around the time of conception and during pregnancy offers a means of protection to the uninfected partner. Unfortunately, data relating to the safety of PrEP specifically with regard to the developing foetus are limited, and consequently the onus is on the clinician to discuss potential risks and benefits of PrEP initiation or maintenance during pregnancy with the client.

BOX 9: HIV prevention for pre-exposure prophylaxis users.

<b>General factors to consider:</b>	
<ul style="list-style-type: none"> <li>• accessibility of condoms and compatible water-based lubricant should be addressed</li> <li>• no single HIV risk reduction intervention is likely to suit all users</li> <li>• combinations of prevention options, tailored to address specific risks, should be offered ('menu of prevention choices'), inclusive of biomedical and psychosocial/behaviour change interventions</li> <li>• prevention options are likely to increase as new evidence becomes available</li> </ul>	
<b>Biomedical:</b>	
<ul style="list-style-type: none"> <li>• male or female condoms and compatible lubrication</li> <li>• access to frequent HIV testing</li> <li>• early access to ART</li> <li>• post-exposure prophylaxis</li> <li>• pre-exposure prophylaxis</li> <li>• voluntary medical male circumcision</li> <li>• STI screening and treatment</li> <li>• needle syringe exchange and opioid substitution therapy for people who inject drugs</li> </ul>	
<b>Psychosocial:</b>	
<ul style="list-style-type: none"> <li>• education: risk and safer sex practices</li> <li>• regular HIV counselling and screening</li> <li>• reducing number of sex partners</li> <li>• reducing alcohol and substance abuse</li> <li>• addressing mental health needs</li> <li>• couple counselling and programming</li> <li>• harm reduction counselling and support for clients who use drugs</li> </ul>	

PrEP trials involving heterosexual women excluded pregnant women from enrollment, and those who fell pregnant during the conduct of the study were discontinued from PrEP. One study of 46 uninfected women in serodiscordant relationships demonstrated no adverse effects on the pregnancy or cases of HIV transmission when TDF was used around the time of conception. There are several ongoing demonstration projects that will allow women to continue PrEP if they fall pregnant, which will provide some data to inform future recommendations. In addition, the Antiretroviral Pregnancy Registry shows no evidence of adverse outcomes amongst infants exposed to these medications when used as antiretroviral therapy *in utero*.

In serodiscordant couples, the infected partner should be initiated on ART and virologically suppressed, ideally for 6 months, before any attempts to conceive.

In South Africa, the use of TDF/FTC as PrEP in pregnant or breastfeeding women is contra-indicated. However, as the risk of seroconversion during pregnancy is high, the risks and benefits of PrEP should be discussed with potential PrEP users, allowing these women at high risk of HIV acquisition to make an informed decision regarding PrEP use.<sup>2</sup>

Exposure to PrEP via breast milk has not been extensively studied. However, HIV-negative babies born to HIV-positive mothers on PMTCT B+ programmes and lifelong ART are exposed to TDF/FTC. The risk of HIV infection against the risk of ARV exposure to the infant should frame a discussion with a potential PrEP user who is pregnant or is planning conception.

## The future of pre-exposure prophylaxis

Whilst recommendations for safe and effective PrEP use in correctly identified users to prevent HIV acquisition are strong, questions still remain on optimising the user selection, the ideal distribution platform and optimal monitoring schedule. Ongoing health service research aims to address these knowledge gaps. For more information, consult the AVAC website <http://www.avac.org/prevention-option/prep>.

Please report adverse events occurring on PrEP to the National Adverse Drug Event Monitoring Centre, which is housed in the Division of Pharmacology at the University of Cape Town. The reporting guideline is available at: [http://www.mccza.com/genericDocuments/2.11\\_ADR\\_reporting\\_Jun11\\_v2.doc](http://www.mccza.com/genericDocuments/2.11_ADR_reporting_Jun11_v2.doc).

## Acknowledgements

### Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

## Authors' contributions

M.M. is the corresponding author and prepared the first draft of the manuscript. L.-G.B. and K.R. co-chaired a meeting of the PrEP Guideline Development Committee, where the principles of the guideline were agreed upon. The remaining authors were involved in the discussions that guided the development of the manuscript and also reviewed the first draft. All authors developed the recommendations.

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## APPENDIX 4: SAMPLE QUESTIONNAIRE ASSESSING BELIEFS, ATTITUDES AND KNOWLEDGE OF

### DOCTORS REGARDING HIV PrEP

## Demographic information

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2. Which province and suburb in South Africa do you currently practise in?

3. Do you identify as:

*Mark only one option*

- ☒ Male  
☐ Female

4. What type of doctor are you?

*Mark only one option*

- ☒ General practitioner/family physician  
☐ Infectious disease specialist  
☐ General internist  
☐ Other

5. If other, please specify:

6. In what type of setting do you practise predominantly?

*Mark only one option*

- ☒ Private practice  
☐ Community hospital  
☐ Academic hospital  
☐ Community health centre  
☐ Walk-in clinic  
☐ Sexual health clinic  
☐ Other

7. If other, please specify:

8. What percent of your work time do you spend on clinical activities?

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9. What percent of your work time do you spend on administrative activities?

---

10. What percent of your work time do you spend on research activities?

---

11. What percent of your work time do you spend on Public Health?

---

12. What percent of your work time do you spend on teaching?

---

13. I identify as a specialist in HIV care.

*Mark only one option*



Strongly disagree



Disagree



Neutral



Agree



Strongly agree

14. How many years have you been an independent practitioner?

---

15. What proportion of your patient population is HIV positive (please enter an estimated percentage)?

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16. What proportion of your patient population is HIV negative but at high risk of HIV acquisition (please enter an estimated percentage)?

---

17. Does your practice serve a substantial population of any of the following groups.  
*check all that apply*

- ☐ Gay, bisexual and other men who have sex with men
- ☐ Transgender individuals
- ☐ People who use injection drugs
- ☐ Prison inmates
- ☐ Sex workers and their clients
- ☐ Women

## Questions about HIV PrEP

Pre-exposure prophylaxis for HIV prevention

PrEP is a new HIV prevention method that has recently been found effective in clinical trials. Truvada has also been approved for use as PrEP on 08 December 2015 by the Medicines Control Council of South Africa. It involves an HIV-negative individual taking anti-retroviral drugs in an effort to reduce their risk of becoming infected with HIV. Using the current strategy, PrEP drugs (typically tenofovir/emtricitabine (Truvada) and/or tenofovir on its own) need to be taken daily on a regular basis —starting before and continuing after exposure to HIV.

Clinical trials show that PrEP is only partially protective against HIV infection and much less so if not taken consistently. People using PrEP would need to commit to regular doctor's appointments to monitor adverse effects and adherence. Patients would also require regular testing for HIV and other sexually transmitted infections.

In this survey, PrEP specifically refers to the daily use of anti-retroviral pills by people who are HIV-negative, also known as oral PrEP. PrEP is not the same as post-exposure prophylaxis or PEP, which is the daily use of antiretroviral pills for 28 days AFTER a potential exposure.

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### 18. How would you describe your current knowledge of HIV pre-exposure prophylaxis?

- ☐ *Mark only one option*
- ☐ Not familiar at all (first time I hear about it) *Skip to question 31.*
- ☐ Somewhat familiar (I am aware of PrEP and the existence of clinical trials but not of their details) *Skip to question 19.*
- ☐ Very familiar (I am aware of the details of recent clinical trials) *Skip to question 19.*

### 19. Where did you hear about PrEP?

- check all that apply*
- ☐ Peer-reviewed medical journal
- ☐ HIV/AIDS-related or other medical conference
- ☐ Workshop, lecture or seminar
- ☐ Colleagues
- ☐ Client/patient

- ☐ Website or blog
- ☐ Other

**20. If other, please specify:**

**21. Do you have any thoughts/opinions/concerns on the use of oral PrEP for the prevention of HIV infection?**

---

**22. Have you ever been questioned by a patient about pre-exposure prophylaxis (PrEP)?**

*Mark only one option*

- ☒ Yes
- ☐ No

**23. Who has asked you about PrEP?**

*check all that apply*

- ☐ Men who have sex with men
- ☐ People in serodiscordant relationships
- ☐ Person/s working as commercial sex workers
- ☐ Person/s using intravenous drugs
- ☐ Other

**24. If other, please specify:**

**25. Have you ever prescribed PrEP as an HIV prevention option to a patient?**

*Mark only one option*

- ☒ Yes
- ☐ No

**26. If you answered yes to the previous question, how many times have you prescribed PrEP**

in the last year?

---

**27. To whom have you prescribed PrEP?**

*check all that apply*

- ☐ Men who have sex with men
- ☐ People in serodiscordant relationships
- ☐ Person working as a commercial sex worker
- ☐ Person using intravenous drugs
- ☐ Other

**28. If other, please specify:**

**29. If you have spoken to a patient about PrEP, were you generally:**

*Mark only one option*

- ☐ Unenthusiastic
- ☐ Neutral
- ☐ Enthusiastic

**30. If any of your patients obtained PrEP off-label, do you know how they obtained it?**

*check all that apply*

- ☐ Off-label prescription by a doctor
- ☐ Internet purchase
- ☐ From an HIV positive partner or friend
- ☐ Other informal channels (eg obtained on the street)
- ☐ Unsure

## Opinions about PrEP

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**31. Knowing what you know about PrEP now, would you prescribe PrEP for a patient at high risk of infection?**

*Mark only one option*

- ☒ Yes
- ☐ No
- ☐ Maybe

**32. To what extent do you agree with the following statements:**

*Mark only one option per row*

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
PrEP is dangerous and should not be pursued further	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
PrEP is a useless distraction	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
PrEP may be useful but is not ready to be made more widely available	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
PrEP is an exciting new prevention tool and should be made more widely available as soon as possible	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>

**33. What is the MINIMUM level of protection you would consider reasonable for PrEP use to be recommended to individuals at high risk of HIV infection?**

**Please report a percentage value. For example, "x" = x % reduction in HIV Infection.**

---

**34. PrEP will likely be recommended to individuals at high risk for HIV infection. How would you define high risk in this context?**

*check all that apply*

- ☐ Gay, bisexual or other men who have sex with men
- ☐ Individuals with a large number of sexual partners
- ☐ Individuals with a history of one or more STIs
- ☐ Individuals who have sex under the influence of drugs
- ☐ Individuals who have used post-exposure prophylaxis (PEP) before (ie have taken antiretroviral drugs AFTER exposure to HIV to prevent becoming infected)
- ☐ People who use injection drugs and other people who may share needles
- ☐ HIV negative individuals who are sexually active with HIV positive partners on an ongoing basis
- ☐ Individuals who exchange sex for money, goods or housing
- ☐ Individuals who belong to any population with a high incidence of HIV
- ☐ Other

**35. If other, please specify:**

**36. In the context of the previous question, how would you define a large number of sexual partners? (please enter minimum number of partners per month)**



37. In the context of the previous question, how would you define regularly engaging in unprotected sex? (please enter minimum number of unprotected sexual encounters per month)

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38. According to one study among men who have sex with men (MSM), oral PrEP provided 44% protection against HIV infection overall and 73% protection in participants who used PrEP consistently (ie took the medication on a regular schedule and did not miss any doses). Other studies show similar levels of protection in heterosexual men and women. Considering this level of protection, do you believe the Medicines Control Council was right to approve PrEP for use in South Africa?

*Mark only one option*

- ☒ Yes  
☐ No  
☐ Maybe

39. Who do you think should pay for PrEP in South Africa?

*check all that apply*

- ☐ Public drug plans ( the government)  
☐ Private drug plans  
☐ The taxpayer through eg a National Health Insurance  
☐ The patient using PrEP  
☐ Other

40. If other, please specify:

41. In what kind of settings do you think PrEP should be prescribed?

*check all that apply*

- ☐ Dedicated PrEP clinics  
☐ Incorporated into STI or HIV clinics  
☐ Individual doctor's offices (like any other health issue)  
☐ Other

42. If other, please specify:

43. The following issues have been raised as important considerations for the implementation of oral PrEP. To what extent do each of these issues shape your beliefs and opinions about whether or not PrEP should be made widely available in South Africa?

Mark only one option per row

	not at all important	of little importance	neutral	somewhat important	very important
Efficacy (ie the % decrease in risk of HIV infection)	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
Risk for development of antiviral drug resistance if a person using PrEP becomes infected	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
Potential side effects and their severity	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
Risk that PrEP may increase risk-taking (behavioural disinhibition)/ risk compensation	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
Risk that patients may not adhere to necessary monitoring and testing while taking PrEP	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
Risk that patients may not take PrEP medications as directed, thus reducing its efficacy	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
Cost-	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>

effectiveness  
of PrEP  
Unequal  
access for  
certain groups  
if funding for  
PrEP  
medication is  
out-of-pocket  
or through  
private  
insurers



44.

Please rank the THREE considerations you believe are the MOST IMPORTANT in order from LEAST to MOST important.

Mark only one option per row

	Most important	Second most important	Third most important
Efficacy (ie the % decrease in risk of HIV infection)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Risk for development of antiviral drug resistance if a person using PrEP becomes infected	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Potential side effects and their severity	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Risk that PrEP may increase risk-taking (behavioural disinhibition)/ risk compensation	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Risk that patients may not adhere to necessary monitoring and testing while taking PrEP	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Risk that patients may not take PrEP medications as directed, thus reducing its efficacy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Cost-effectiveness of PrEP	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Unequal  
access for  
certain groups  
if funding for  
PrEP  
medication is  
out-of-pocket  
or through  
private  
insurers



**45.** Do you have any other concerns that were not mentioned that you feel are important?

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**46.** After considering the issues above, to what extent do you agree with the following statements?

*Mark only one option per row*

strongly  
disagree

disagree

neutral

agree

strongly agree

Policy makers  
have an ethical  
obligation to  
make available  
any intervention  
that could  
decrease an  
individual's risk  
of becoming  
infected with  
HIV  
PrEP could lead  
to the  
"medicalization"  
of HIV  
prevention and  
take focus away  
from other,  
more important  
prevention



efforts  
Investing in  
PrEP would be  
an appropriate  
use of  
healthcare  
resources  
There is not  
enough  
evidence  
available to  
justify making  
PrEP widely  
available in  
South Africa

<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>

**47. Do you think some of the patients you serve would benefit from PrEP?**

*Mark only one option*

- ☒ Yes
- ☒ No
- ☒ Maybe

**48. To what extent do you agree with the following statements?**

*Mark only one option per row*

strongly disagree      disagree      neutral      agree      strongly agree

I have enough  
knowledge of  
PrEP to make  
informed  
prescribing  
decisions  
I think that  
information  
about PrEP has  
been  
adequately  
disseminated  
among  
doctors

<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>
<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>

**49. The following media would be useful to me in learning more about PrEP:**

*check all that apply*

- ☐ Access to papers from peer-reviewed journals
- ☐ Website
- ☐ CPD event or workshop
- ☐ Online learning modules
- ☐ Brochure
- ☐ N/A ( I do not need more information about PrEP)
- ☐ Other

**50. If other, please specify:**

**51. What are the current barriers against prescribing PrEP?**

*check all that apply*

- ☐ I am not familiar enough with PrEP to prescribe it
- ☐ I am unsure of which patients to prescribe it to
- ☐ I do not think my patients would be interested in PrEP as an option
- ☐ My patients are unable to get the drug costs covered
- ☐ I do not feel there is sufficient data to support its use
- ☐ Other

**52. If other, please specify:**

**53. What supports would your practice need before implementing PrEP?**

*check all that apply*

- ☐ Adherence counselling by trained counsellor
- ☐ Continuing medical education on new evidence for PrEP
- ☐ Nursing support for ongoing patient counselling, routine STI and HIV testing and monitoring for adverse effects
- ☐ Other

**54. If other, please be as specific as possible**

**55. What do you think is needed, in general, before PrEP is made more widely available as an**

**HIV prevention strategy?**

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**56. Any further thoughts?**

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Thank you very much for taking the time to fill out this survey.

After pressing the “done” button below responses will be saved and you will no longer have the option to withdraw from the study.

A copy of the consent form can be downloaded for your records by clicking on the following link:

<https://drive.google.com/file/d/0B-MXAuKr2aLOZVBCSFFvaDBXV28/view?usp=sharing>

If you would like to download the 2016 South African guidelines on the use of Truvada as PrEP, you can do so by clicking on the following link:

<https://drive.google.com/open?id=0B-MXAuKr2aLOTHBtMIE0ZGp4V28>

To enter the draw to win an Ipad, you may email Dr Llewellyn Fleurs by clicking on the link below:

[llewiwanttheipad@gmail.com](mailto:llewiwanttheipad@gmail.com)

Please send your name, surname, suburb and province you practise in, and a contact number in the email.

If there are any questions you may contact the Principal Investigator Professor Linda-Gail Bekker at [linda-gail.bekker@hiv-research.org.za](mailto:linda-gail.bekker@hiv-research.org.za) or (021) 406 6970 or Dr Llewellyn Fleurs at [llewellyn.fleurs@hiv-research.org.za](mailto:llewellyn.fleurs@hiv-research.org.za) or (021) 650 3641 during office hours.



## **APPENDIX 5: BUDGET FOR PROJECT**

### **BUDGET FOR DISSERTATION PROJECT (FLRLLE001)**

ITEM	QUANTITY	PRICE
Creating online survey	1	4188.00
Sending out emails to doctors	14325	0.00
Ipad for competition	1	13999.00
<b>TOTAL</b>		<b>18187.00</b>

### **NOTES:**

Study will be conducted using no official funding.  
The Ipad will be bought through the Desmond Tutu  
Research Foundation.

## **APPENDIX 6: UCT ETHICS APPROVAL LETTER**



**UNIVERSITY OF CAPE TOWN**  
**Faculty of Health Sciences**  
**Human Research Ethics Committee**



Room E53-46 Old Main Building  
Groote Schuur Hospital  
Observatory 7925  
Telephone [021] 406 6492  
Email: [sumayah.arietdien@uct.ac.za](mailto:sumayah.arietdien@uct.ac.za)  
Website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms)

10 June 2016

**HREC REF: 207/2016**

**Prof LG Bekker**  
Desmond Tutu HIV Foundation  
IIDMM  
FHS

Dear Prof Bekker

**PROJECT TITLE: TRUVADA APPROVED AS HIV PrEP: ARE SOUTH AFRICAN DOCTORS READY? (MPH CANDIDATE - DR L FLEURS)**

Thank you for your response letter, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**Approval is granted for one year until the 30 June 2017.**

Can the investigator please insert a mechanism for a doctor completing the survey to download a copy of the participant information 1<sup>st</sup> page of the survey for their records, or to have the option of getting a copy of the participant information sent to their email address? Participants may want to keep a record of this, and it is generally our standard to get participants a copy of the patient information and consent to take home with them for future reference.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms))

***We acknowledge that the following student, Dr Llewellyn Fleurs will also be involved in this study.***

**Please quote the HREC REF in all your correspondence.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur

HREC 207/2016

Yours sincerely

pp T. Burgess

**PROFESSOR M BLOCKMAN**

**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE**

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 207/2016

## **APPENDIX 7: JOURNAL OF INTERNATIONAL AIDS SOCIETY**

### **GUIDELINES**

NEW JIAS  
SPECIAL  
ISSUE

HIV EPIDEMICS AMONG TRANSGENDER  
POPULATIONS: THE IMPORTANCE OF A  
TRANS-INCLUSIVE RESPONSE  
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## **Submissions**

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- » [Author Guidelines](#)
- » [Copyright Notice](#)
- » [Privacy Statement](#)

### **Online Submissions**

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Registration and login are required to submit items online and to check the status of current submissions.

## Author Guidelines

The *Journal of the International AIDS Society (JIAS)* welcomes submissions on HIV-related topics from various disciplines and accepts submissions of Original Research Articles, Short Reports, Reviews, Debates, Commentaries, Letters to the Editor and Viewpoints. Please carefully read through the Instructions for Authors and prepare your manuscript according to the guidelines; structure your manuscript based on the chosen article category. Manuscripts that do not follow the instructions may be returned to the authors for re-formatting. Submissions must be an original contribution, and the authors must guarantee that the content has not been previously published and is not considered for publication elsewhere. The JIAS levies a publication fee on all accepted articles to fund open-access publication. For information on editorial policies and processes, see the [About JIAS](#) page. For scientific writing resources and support, see [Writing resources](#).

### **Information prior to submission**

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[Ethical policies](#)

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[Open access policy](#)

[Publication fees](#)

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[Protein and nucleotide sequences](#)

[Mass spectrometry](#)

[Structures](#)

[Chemical structures and assays](#)

[Functional genomics data \(such as microarray or CHIP-Seq data\)](#)

[Computational modelling](#)

[Plasmids](#)

## **INFORMATION PRIOR TO SUBMISSION**

### **Aims and scope**

The JIAS welcomes submissions on HIV-related topics from across all scientific disciplines, including but not limited to:

- Basic and biomedical sciences
- Behavioural sciences and epidemiology
- Clinical sciences
- Health economics and health policy
- Operations research and implementation sciences
- Social sciences and humanities, including political sciences and media

The JIAS places high priority on submissions from operational research and implementation science as publication of such material can provide valuable information on various algorithms for monitoring and providing support for comprehensive, yet affordable and sustainable treatment, prevention and care programmes in different contexts.

Submission of HIV research carried out in low- and middle-income countries is strongly encouraged.

The JIAS accepts submissions in the categories of Research, Short Report, Review, Debate, Commentary and Letter to the Editor.

### **Ethical policies**

The JIAS is a member of the [Committee on Publication Ethics \(COPE\)](#) and endorses the World Association of Medical Editors' (WAME's) [Policy Statement on Geopolitical Intrusion on Editorial Decisions](#). All submitted manuscripts are scanned for plagiarism and may be rejected if significant overlap with other published material is detected. Work presented in submitted manuscripts may not have been previously published; nor may the same manuscript be submitted for consideration to another journal simultaneously. Any misconduct by authors in reporting their data, for example, falsification, will lead to rejection of their manuscript and other consequences decided on by the Editors. Please see [COPE](#) and [International Committee of Medical Journal Editors \(ICMJE\)](#) for further information on ethical issues in publishing.

### *Authorship*

It is understood that all authors listed on submitted manuscripts have read and agreed to its content, and meet the authorship requirements as detailed by ICMJE [here](#). In brief, contributors can be listed as authors if they: 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; AND 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; AND 3) have given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for

appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All contributors who do not meet the criteria for authorship should be listed in the Acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help or writing assistance, or a head of department, who provided only general support.

#### *Ethical approval*

Experimental research described in the manuscript must have been performed with the approval of an appropriate ethics review board. Research carried out on humans must be in compliance with the [Helsinki Declaration](#), and any experimental research on animals must have followed internationally recognized guidelines. A statement on the ethical aspects, including the consent procedure followed, must be included in the Methods section of the manuscript. The Editors may reject manuscripts where the research has not been carried out within an ethical framework. For all articles that include information or photographs relating to individuals, written and signed consent from each patient to publish must also be made available if requested by the Editors. Confidentiality of study participants must be ensured at all stages of research and reporting.

#### *Competing interests*

Authors are required to submit a statement on competing interests, which exist when personal or financial relationships with persons or organizations may influence the interpretation of the data or how the author's work is presented. For details, see ICMJE's policy on competing interests [here](#). In brief, all financial competing interests must be disclosed in this statement (reimbursements, fees, funding, salary payments from or ownership of any stocks or shares in an organization that may in any way gain or lose financially from the publication of the manuscript, either now or in the future, or applications for patents relating to the content of the manuscript), as well as non-financial competing interests (such as political, personal, religious, ideological, academic and/or intellectual interests) that are related to the work submitted. The competing interest statement should be included in the manuscript and will be published in the final article. If no competing interests exist, please state in this section, "The author declare that they have (or The author declares that he/she has) no competing interests."

#### *Copyright and libel*

Legal responsibility to ensure that no material is published that infringes copyright or that includes libellous or defamatory content lies with the Journal of the International AIDS Society's publisher, the International AIDS Society. If a manuscript is judged by the journal Editors to include potentially libellous content, authors will be requested to adjust wording as necessary.

#### *Commercial writers and editors*

The involvement of scientific (medical) writers or anyone else who assisted with the preparation of the manuscript content should be acknowledged, along with their source of funding, as described in the European Medical Writers Association (EMWA) [guidelines](#) on the role of medical writers in developing peer-reviewed publications.

## **MANUSCRIPT PREPARATION**

### **Standards of reporting**



The *JIAS* endorses international standards of reporting. Please see the [Uniform Requirements for Manuscripts Submitted to Biomedical Journals](#) guidelines produced by ICMJE as a reference standard of reporting. Authors are also referred to the [EQUATOR](#) network website for further information on the available reporting guidelines for health research, and the [MIBBI](#) Portal for prescriptive checklists for reporting biological and biomedical research where applicable. A number of checklists are available for various study designs, including randomized controlled trials ([CONSORT](#)), systematic reviews ([PRISMA](#)), observational studies ([STROBE](#)), meta-analyses of observational studies ([MOOSE](#)) and diagnostic accuracy studies ([STARD](#)). For systematic reviews, an additional file should be provided by the authors listing all details concerning the search strategy. Please refer to the [Cochrane Reviewers' Handbook](#) for an example of how a search strategy should be presented.

Guidelines on mutation nomenclature are provided by the [Human Genome Variation Society](#), and authors should use the recommended gene name by referring to the appropriate genetic nomenclature database, for example, HUGO for human genes, and the International Committee on Standardized Genetic Nomenclature for Mice. When describing human phenotypes, please use standardized terms, such as those proposed by the Elements of Morphology working group (see <http://research.nhgri.nih.gov/morphology/index.cgi>).

Contributions from pharmaceutical companies or other commercial organizations should follow the [Good Publication Practice guidelines for pharmaceutical companies](#), which also apply to any companies or individuals that work on industry-sponsored publications, such as freelance writers, contract research organizations and communications companies.

The *JIAS* supports international standards of reporting of trials, in particular, prospective registering and numbering of clinical trials. Clinical trials are defined by the World Health Organization as all phase I to IV trials, which are research studies that prospectively assign human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Trials need to be registered prior to submission in a suitable, publicly available registry. Links to existing registries can be found through ICMJE [here](#) or through the primary registers that participate in the [WHO International Clinical Trials Registry Platform](#). The trial registration number should be included as the last line of the manuscript Abstract.

### **File formats**

Accepted file formats are OpenOffice, Microsoft Word, RTF or WordPerfect; in addition, a PDF copy of the manuscript needs to be prepared. Tables and figures should be inserted in the main text. Additional files, such as supporting information or large datasets, can be submitted in any file format and should be uploaded as a separate file. Footnotes are not allowed.

### **Style and language**

Use line spacing of 1.5 and an easily readable font, for example, Times New Roman, size 12. Do not use underlining, but use of bold and italics is acceptable. Set the text unjustified to the left and use portrait page setup. Your manuscript must contain line numbers to facilitate editors' and reviewers' comments. All submissions must be in UK English (International) and UN-accepted terminology should be followed. No capitalization should be used except for grammatically correct use, official names and titles, and abbreviations. Acronyms should be used sparingly, and not in headings or in the Abstract. Only commonly known acronyms may

be used, and they should be spelt out at first use followed by the abbreviation in brackets. SI units should be used, with litre and molar being permitted.

### **Cover letter**

In the cover letter, please explain why your manuscript should be published in the journal. If necessary, address any issues relating to our editorial policies (see [About JIAS](#)) and declare any competing interests (see [Competing interest](#)).

You can also suggest potential peer reviewers for your manuscript: they should be experts in the field and be able to provide an objective assessment of the manuscript. Any suggested peer reviewers should not have published with any of the authors of the manuscript within the past five years, should not be current collaborators, and should not be members of the same institution. Suggested reviewers will be considered alongside potential reviewers identified by the Editorial team.

Members of the International AIDS Society receive a 15% discount on the publication fee. *Authors should include their valid membership number in the cover letter upon submission.*

### **Title page**

On the title page, you should mention the title of the manuscript, list all authors' names in full, and list any study groups if applicable. Each authors' affiliation should be numbered in superscript consecutively and listed underneath, including department, institution, city and country. The corresponding author should be marked with the symbol § in superscript and full contact details should be provided, including a telephone number with country code. Authors who have contributed equally to the work should be marked with the symbol \* in superscript. Deceased authors should be marked with the symbol ^ in superscript. The email addresses of all authors should be listed by their initials. A list of six to eight keywords should be provided, preferably alternate words to those found in the abstract in order to improve search hits for the article in repositories.

### **Abstract**

The Abstract should not exceed 350 words and should be structured according to the headings of the selected article category (see below), excluding the heading, Discussion for Research articles. Avoid using abbreviations and do not cite references in the Abstract. If you are reporting results from a controlled health care intervention, please include your trial registry, together with your unique identifying number at the end of the Abstract. For randomized controlled trials, follow the [CONSORT extension for abstracts](#).

### **Main text**

More information on the different article categories is provided below, including specific section headings and word limits. Information on the different sections in the manuscript is further detailed below, as well.

### **Article categories**

*Research* - full reports of data from original research studies

Headings: Introduction, Methods, Results, Discussion, Conclusions

Word limit: 3500 words

Numbers of figures and tables: Unlimited

Additional files: Yes

### [Manuscript template](#)

*Short report* - brief reports of data from original research, such as follow-up or confirmatory studies, case series and negative results

Headings: Introduction, Methods, Results and discussion, Conclusions

Word limit: 2500 words

Numbers of figures and tables: 4

Additional files: No

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*Review* - comprehensive, authoritative descriptions and summaries of a specific subject area providing a systematic and substantial overview of the field

Headings: Introduction, Methods (if applicable), Results and discussion (if applicable, otherwise Discussion only), Conclusions

Word limit: 5000 words

Numbers of figures and tables: Unlimited

Additional files: Yes

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*Debate* - presentation of an evidence-based argument

Headings: Introduction, Discussion, Conclusions

Word limit: 3500 words

Numbers of figures and tables: 4

Additional files: No

[Manuscript template](#)

*Commentary* - focused and opinionated articles on important and timely issues

Headings: Introduction, Discussion, Conclusions

Word limit: 2500 words

Numbers of figures and tables: 1

Additional files: No

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*Letter to the Editor* - comments on and responses to published articles

Headings: None

Word limit: 500 words

Numbers of figures and tables: None

Additional files: No

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*Viewpoint* - constructive, stand-alone views on current topics

Headings: None

Word limit: 1000 words

Numbers of figures and tables: 1

Additional files: No

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### **Article sections**

*Introduction*

The Introduction section should introduce the topic to readers without specialist knowledge in that area and must clearly outline the current state of knowledge in this field, the motivation and the aim of the study or the article.

### *Methods*

The Methods section should include all information necessary to repeat the study, in particular, the study design, how data was collected and analyzed, clarifying the choice of methods that were made. If applicable, you should describe the setting of the study, the dates the study were conducted, and the sample or participants, as well as necessary power calculations and materials, including statistical packages, used. Interventions and programmes should be described in detail. Generic names for drugs or any molecules should be used.

All studies involving humans or animals require a statement on ethical approval, and for the former, the consent procedure that was followed. Please include the names of the ethics review board(s) that approved the study. If the research study was specific to one sex/gender, the reasons for this should be clearly stated.

### *Results*

This section should include only data and findings from the authors' study. Presentation of statistical results should mention confidence intervals and levels of significance where appropriate. Quotes from qualitative study participants of less than three lines should be quoted in the text using quotation marks. For quotes longer than three lines, place the quote in a separate, indented paragraph and introduce it with a colon. No quotation marks are needed in this case. Details of the participant can be added in round brackets following the quote, but should not contain identifiable information to ensure confidentiality. Clarifications within the quotation should be placed in square brackets.

Submitting authors are strongly encouraged to include data disaggregated by sex (and, whenever possible, by race) and provide a comprehensive analysis of gender and racial differences. The authors should include the number and percentage of men, women and, if appropriate, transgender persons who participated in the research study. Anatomical and physiological differences between men and women (height, weight, body fat-to-muscle ratios, cell counts, hormonal cycles, etc.), as well as social and cultural variables (socio-economic, education, access to care, etc.), should be taken into consideration in the presentation of data and/or analysis of the results.

### *Discussion*

In the Discussion section, you should discuss your main findings and place these within the context of the current body of knowledge in the field. Limitations of the study, for example, selection bias, can also be discussed, and should address how these influence the results and conclusions. If statistically significant differences were found between men and women or between different racial or cultural groups in the effects of the studied intervention, the implications, if any, for clinical and/or public health should be adequately discussed.

### *Conclusions*

In your Conclusions section, state your key messages from the study and explain their importance and relevance, as well as implications. Future studies and recommendations can be included in this section. The conclusions drawn must be strictly based on the data

provided.

### **Figures**

Figures should be integrated into the text at the appropriate place. Figures should be cropped as closely as possible and have the header: "Figure 1. Title of figure". All figures need to be cited in the text in consecutive order. Legends should be provided underneath the figures, listing any abbreviations or meanings of symbols used. If several figures are included, please ensure that symbols are used consistently. Sufficient information needs to be provided for the figure to stand alone, including labels of axes. Please ensure that figures are legible in black and white print and also compatible with colour blindness. If figures are copied or adapted from another source, authors must seek permission prior to publication and these should be clearly cited as such. If the complete figure spans more than one page, authors should upload the figure as an additional file instead. High-resolution illustrations are recommended for optimal viewing performance in the final article.

### **Tables**

Tables must be created within the word file in the correct place and should have the header: "Table 1. Title of table". All tables should be cited in the text in consecutive order. The tables should not contain colour or shading, and no vertical, visible lines. A legend can be provided underneath the title, listing any abbreviations or meanings of symbols used. If several tables are included, please ensure that symbols are used consistently. If tables are copied or adapted from another source, permission must be sought by the authors prior to publication and these should be clearly cited as such. If a table spans more than one page, authors may want to consider uploading the table as an additional file instead.

### **References**

All external sources of information should be referenced within the text, the tables and figures, using consecutive numbering in square brackets, e.g. [1], [3-5], [3,4]. The references should be up to date and adequately reflect the current state of knowledge in the field. Citation bias, for example, by country or point of view must be avoided. Numbers of references are unlimited for all article categories and should be formatted in standard Vancouver style; see [Sample references](#) from ICMJE. Unpublished observations, personal communications and manuscripts currently under consideration should be cited in the text in round brackets and not in the reference list.

## **ADDITIONAL SECTIONS FOR MANUSCRIPTS**

### **Competing interests - required**

Please use authors' initials, and list any competing interests for each author. If there are no declarations to be made, you should state that the authors have (or the author has) no competing interests to declare. See the [Competing interests](#) section for further details.

### **Acknowledgements and funding - required**

It is the authors' responsibility to seek permission from persons to be mentioned in the Acknowledgements section. Please acknowledge anyone who contributed to the study and/or manuscript preparation, but who does not meet the authorship criteria (see guidelines on Authorship). The contribution of medical/scientific writers or language editors must be listed, including their source(s) of funding. For the study and the manuscript, the source(s) of funding should be listed and the role of the funding bodies detailed.

**Authors' contributions** - required

The individual contributions of each author must be specified in the Authors' contributions section. Please use authors' initials and state that all authors have read and approved the final manuscript. See the [Authorship](#) section for further details.

**Additional files** - optional

Supporting data or supplementary files can be included in the submission as additional files. A section listing the additional files numbered consecutively should be provided as "Additional file 1", "Additional file 2", etc. and all files need to be referenced in the main text in round brackets. Please specify the file format used and a short description of the data under each title. Additional files will be linked to the published article in the same format as originally submitted by the authors, but will not be displayed within the article. Please use file formats that readers can access using free or widely available tools.

**Author information** - optional

This section can be used to include additional information on the author(s) that may be useful for readers' interpretation of the article and their understanding of the viewpoint presented.

**List of abbreviations** - optional

A list of all abbreviations presented in alphabetical order can be provided in a separate section.

Table 4: Summary of model building

MODEL	LOG LIKELIHOOD	LR TEST		AIC
		chi <sup>2</sup>	p value	compared to
A. Constant	-21.61	0	N/A	N/A
<i>Adding potential confounders</i>				
B. Years of experience (10 year Increments)	-21.55	0.14	0.71	Constant
Female sex	-21.57	0.1	0.76	constant
Self-identified specialist in HIV care	-21.57	0.08	0.77	constant
Infectious disease specialist	-20.86	1.5	0.22	Constant
Academic setting	-20.52	2.2	0.14	Constant
Private practice	.Perfect success*			
Time spent in clinical work (10% increments)	-20.80	1.62	0.20	Constant
Time spent in administrative work (10% increments)	-21.59	0.04	0.84	Constant
Time spent in research (10% increments)	-19.53	4.16	<b>0.04</b>	Constant
Time spent in public health (10% increments)	-21.61	0.01	0.92	Constant
Time spent in teaching (10% increments)	-19.25	4.73	<b>0.03</b>	Constant
HIV positive patients (10% increments)	-21.38	0.46	0.49	Constant
High risk HIV negative patients (10% increments)	-21.52	0.19	0.66	Constant
High percentage of MSM patients	-21.09	1.05	0.30	Constant
High percentage of transgender patients	Perfect success*			
High percentage of patients who inject drugs	Perfect success*			
Prison inmates as patients	-21.53	0.17	0.68	Constant
Sex workers as patients	Perfect success*			
Female patients (serodiscordant partners)	Perfect success*			
Previous knowledge of HIV	-21.48	0.28	0.60	Constant



<b>PrEP</b>					
Knowledge of PrEP from journals	-20.51	2.20	0.14	Constant	N/A
Knowledge of PrEP from conferences	-21.07	1.08	0.30	Constant	N/A
Knowledge of PrEP from seminars	-20.64	1.94	0.16	Constant	N/A
Knowledge of PrEP from discussion with colleagues	-21.58	0.07	0.79	Constant	N/A
Knowledge of PrEP from patients	Perfect success*				
Knowledge of PrEP from websites	-21.27	0.70	0.40	Constant	N/A
Other sources of knowledge about PrEP	Perfect success*				
Being asked about PrEP from Any patient	-20.33	2.56	0.11	Constant	N/A
Efficacy rated as most important	-20.75	1.73	0.19	Constant	N/A
Development of HIV resistance rated as most important	-21.60	0.01	0.90	Constant	N/A
Development of side effects rated as most important	Perfect success*				
Patient disinhibition rated as most important	-21.44	0.35	0.55	Constant	N/A
Clinical monitoring of patients rated as most important	-21.60	0.03	0.87	Constant	N/A
Patient compliance rated as most important	-21.38	0.47	0.49	Constant	N/A
Cost-effectiveness rated as most important	-20.34	2.54	0.11	Constant	N/A
Patient access to Truvada rated as most important	-21.34	0.54	0.46	Constant	N/A
Adherence counselling= facilitating factor	-21.55	0.13	0.72	Constant	N/A
Continuing medical education= facilitating factor	-21.32	0.59	0.44	Constant	N/A
Nursing support= facilitating factor	-21.18	0.87	0.35	Constant	N/A
Other facilitating factors	-21.46	0.32	0.57	Constant	N/A
<hr/>					
<i>Adding potential risk factors</i>					
<b>C. Time spent in teaching+ time spent in research</b>	-17.92	2.65	0.10	Time spent in teaching	41.84
<hr/>					

\*omitted from model